RATIONALE FOR SEPSIS MANAGEMENT IN IMMUNOCOMPETENT ADULTS

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SUMMARY

In recent years the recognition and management of sepsis has been confounded by poor definitions, a blunted response to infection in a variety of patient populations and lack of appreciation of the principles of antimicrobial chemotherapy. These factors have lead to widespread antibiotic misuse resulting in increased treatment cost, poor patient outcome and emergence of antibiotic resistance. This article aims to highlight modern definitions of the sepsis syndrome and their limitations. The optimum use of antibacterials will be discussed in the context of hospital management of immunocompetent adults with non-travel related infections. Antibiotic policies supported by regular education, training and feedback have a major part to play in the management in hospitals of patients with infections.

INTRODUCTION

'When in a fever not of the intermittent type dyspnoea and delerium come on, the case is mortal'. (Hippocratic aphorism, the fifth century BC)[1]

All hospital specialists to a greater or lesser degree manage patients with infection. Although many infections are acquired in the community, nosocomial infections are of increasing importance, occurring in approximately one in ten patients admitted to hospital in the UK.[2] These infections are quite different from community-acquired infections in that the prevalent organisms and susceptibility patterns are a function of antibiotic prescribing in the hospital and infection control practices such as hand washing.

Antibiotic prescribing in hospitals is widespread. Point prevalence surveys estimate one-third of inpatients are prescribed an antibiotic[3,4] and between 22% and 65% of such prescriptions are either inappropriate or incorrect.[5] There is growing concern and mounting evidence that such widespread and inappropriate antimicrobial prescribing is fuelling the emergence of microbial resistance.[6] Over-use of cephalosporins in particular was responsible for the emergence of *Enterococcus* as an opportunistic pathogen in the 1970s.[7] Subsequent overuse of glycopeptides has been an important factor in the emergence of vancomycin-resistant *Enterococcus*.[7] On this background it is essential that clinicians are able to recognise infection and make an informed and rational choice of antibiotic. This choice should be guided by an awareness of local pathogens and susceptibility patterns, and ideally be guided by local antibiotic policies.

The first part of this review examines the principles of sepsis recognition in the hospitalised patient and outlines the diagnosis of bacterial infection in common clinical scenarios. In the second section strategies for safer antibiotic prescribing in hospitals are outlined. For the purposes of this article the illustrative examples will be confined to hospital-led management of immunocompetent patients with UK-acquired bacterial sepsis. The reader is referred to an earlier article in *Proceedings* which details the management of fever in the returning traveller.[8]

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RECOGNITION OF SEPSIS AND ITS SEVERITY

Poor prognostic features associated with fever were recognised as long ago as the fifth century by the ancient Greeks. Hippocrates noted in his book on Prognostics the way acute diseases, whatever their nature, converged in their clinical manifestations when at the most severe:

> ...the name of any disease may happen not to be described here, for you may know all such as come to a crisis in the afore-mentioned times, by the same symptoms.[1]

Perhaps this was an early reference to the systemic inflammatory response.

Recognising the septic patient is something which doctors think they do innately. In fact, sepsis parameters are poorly recognised by all grades of doctor and the standard of record-keeping pertaining to infection is sub-optimal in many units. For example, in our own Trust we found that one-third of medical patients at any time were receiving antibiotics but only 64% of these had an indication for the antibiotic recorded in the case-notes and only 57% recorded a temperature.[4] This implies that antibiotics are either being prescribed without a clear indication or that little value is placed on case-record documentation and its implications. Contrast this with the recording of information about patients with an acute myocardial infarction where failure to record the patient's blood pressure or electrocardiogram would be patently unacceptable.

Over recent years an attempt was made to formalise definitions of sepsis. This was primarily for the purposes of conducting clinical trials. However a more practical benefit to the clinician is a guide which can improve recognition and management of infection in wards and intensive care units. In addition these definitions can be useful in the assessment and audit of antibiotic prescribing within units.

Markers of sepsis

The 'systemic inflammatory response syndrome' (SIRS), 'sepsis syndrome' and 'septic shock' were defined by Bone in 1991.[9] An attempt is made to grade the severity of an infection by making simple bedside observations. SIRS criteria are met if two or more critical clinical or laboratory signs are present (Table 1). 'Sepsis' is defined as SIRS with clinical evidence of infection. Other conditions such as major trauma, burns, ischaemia or pancreatitis may result in a systemic inflammatory response in the absence of infection. Severe

TABLE 1
Definitions.

Definition
Systemic Inflammatory Response (SIRS) Two or more of the following: 1. Temperature >38 degrees C or <36 degrees C 2. Heart rate >90 beats/minute 3. Respiratory rate >20 breaths/minute or PaCO2<4.3kPa 4. White Cell Count >12,000/mm^3 or <4,000/mm^3
Sepsis Syndrome SIRS plus documented infection.
Severe Sepsis Sepsis associated with hypotension or organ hypoperfusion e.g. confusion, acidosis, renal or liver dysfunction, severe hypoalbuminaemia, thrombocytopenia, leucopenia.
Septic Shock Systolic BP <90mm/Hg despite adequate fluid resuscitation or requiring inotropic or vasopressor agonist for cadiovascular support.

sepsis is defined as the sepsis syndrome in the presence of organ dysfunction.

As patients progress through infection (without SIRS criteria) to the sepsis syndrome, to severe sepsis and septic shock, mortality rises and there is increasing demand for more intensive monitoring and supportive therapy. In two separate studies in the UK and USA carried out in quite different patient populations, mortality was shown to increase from 3-12% in patients with <2 SIRS criteria, to 7-14% for patients with two criteria and 17-36% in patients with four criteria.[10,11] In the USA study, mortality in septic shock was 46%.[10]

The limitations of the SIRS criteria are outlined in Table 2. In every day practice diagnosing infection in the elderly is most problematic since bacteraemic elderly patients have significantly fewer symptoms and signs of infection than young patients;[12,13] however alterations in consciousness and fever are more frequent than in non-bacteraemic elderly controls.[13] In our experience a high index of suspicion for infection should be maintained in elderly patients with recent and rapid deterioration in health. Such patients should be investigated promptly and initially treated in an empirical manner.

TABLE 2
Limitations of SIRS in diagnosing infection in adults.

- Non-specific: ischaemia, inflammatory conditions, post-operative, burns, pancreatitis, etc.
- Insensitive in elderly patients, immunosuppressed, those on beta-blockers, corticosteroids.
- No account of site or type of infection.
- No account of pre-existing morbidity.
- May be absent in deep-seated infections e.g. endocarditis, endovascular infections, osteomyelitis.

Severity markers in pneumonia

Patients with pneumonia may deteriorate rapidly due to hypoxaemia in addition to sepsis. In these patients markers of severity have been well validated.[14,15] Patients with two or more risk factors have a 21-fold increase in the risk of death or the need for intensive care support (Table 3).[14] Patients presenting with these severity markers should be considered early for intensive support. In the elderly an age greater than 85 years, co-morbid disease, impaired motor response, raised creatinine concentrations and abnormalities of vital signs have also been validated as markers of poor prognosis.[16] Administering antibiotics within eight hours of hospital arrival and collecting blood cultures within 24 hours has also been associated with better prognosis in the elderly patient with pneumonia.[17]

TABLE 3
Severity markers in pneumonia.

Independent variables which predict poor outcome:
- Respiratory rate >30 breaths/ minute
- Diastolic blood pressure <60mm/Hg
- Blood Urea >7 mmol/l

Other factors which influence prognosis:
- Age >60 years
- Underlying disease
- Confusion
- Atrial fibrillation
- Multilobar involvement
- PO_2 <=8kPa
- Serum albumin <35g/l
- White cell count <=4,000/mm^3 or >= 20,000/ mm^3
- Bacteraemia
- Failure to administer antibiotics promptly

Severity marker in meningococcal disease

Another special situation is meningococcal infection where specific prognostic factors can be readily identified. A haemorrhagic diathesis, focal neurological signs and age of 60 years or older each independently predict a poor prognosis. Prior appropriate antibiotic therapy is associated with a more favourable outcome.[18] Use of these parameters may aid the clinician in determining not only the patient's prognosis but more importantly the most appropriate site of care with a view to the selection of patients for more intensive supportive therapy and invasive monitoring.

Community versus hospital infection

Defining whether an infection is hospital- or community-acquired is very important as the likely infecting organisms are different and therefore require different empiric antibiotic therapy. Hospital-acquired infection is usually defined as an infection presenting after admission to hospital (usually >48 hours) and not incubating at the time of admission.[2] Such infections are usually device-related (urinary catheter or intravascular device) and are more frequently bacteraemic than community-acquired infections. Increasingly acute medical admissions include patients who are long-term residents in nursing homes. Infections acquired in such settings may be more representative of hospital-acquired infections with a higher prevalence of Gram-negative infections.

INVESTIGATION OF THE PATIENT WITH SEPSIS

Blood culture

Investigations should be directed at identifying a specific

organism or group of organisms, and assessing the severity of the infection. The most important laboratory test in patients with suspected bacterial or invasive fungal sepsis is blood culture. This should be performed on any hospitalised patient with such suspected infection. Blood culture is of particular importance in the diagnosis of hospital-acquired infections where the likely infecting organism is more difficult to predict clinically and bacteraemic infections are common (approximately 6.2% of all hospital-acquired infections).[2] The identification of the organism is of primary importance as this will affect length and route, as well as the choice of antibiotic and will point to a possible removable source of infection e.g. *Staphylococcus aureus* bacteraemia as a result of a central venous catheter-related infection.[19] For the clinician there are three important considerations: the volume of blood drawn, the number of cultures and the site of the cultures.[20] Since the sensitivity of blood culture is related to the volume of blood incubated, it is recommended that at least 10mls of blood should be drawn for each culture (divided between aerobic and anaerobic bottles). Ideally two sets of cultures should be drawn prior to the commencement of antibiotics, and if endocarditis is suspected a further set within 24 hours. Drawing blood from an intravascular device should be avoided unless a device-related infection is suspected and facilities for quantitative culture are available. In this instance specific venepuncture should also be performed.[21]

There are no hard and fast rules about interpreting positive blood cultures. Careful consideration should be given to any positive result before dismissing the growth as a contaminant, and if doubt remains, the doctor who drew the blood should be questioned regarding the site sampled and aseptic technique used. Cultures are likely to be significant if they signal-positive rapidly (within 48 hours) in both bottles or if consecutive positive cultures are received from the same patient, even when an unusual organism is identified. In our experience in immunocompetent adults the coagulase-negative *Staphylococcus* which is identified in one bottle after a week is almost always a contaminant from skin at venepuncture. In contrast, the Gram-negative anaerobe that appears after a similar delay should always be taken seriously since these organisms are often fastidious and rarely contaminants.

The common causes of community- and hospital-acquired bacteraemia in St Thomas's hospital, London over a 20 year period until 1988 are shown in Table 4.[22] In our experience *Staphylococcus aureus* is the most frequent isolate in hospital-acquired infections and Gram-negative organisms and enterococcal species are of increasing importance, particularly in high dependency or intensive care situations where antibiotic exposure is greatest. *Candida* bacteraemia is of increasing importance in hospitals and should be suspected in those patients with persistent fever despite administration of broad spectrum antibiotics, particularly if they have received blood transfusion, parenteral nutrition or have undergone intra-abdominal surgery, or if they are neutropenic or immunosuppressed or, in the intensive care setting, have two or more positive non-contiguous surveillance cultures.[23] Such patients are usually critically ill.

Diagnosing the primary infection

The source of infection should be determined by clinical examination and culture of specific body fluids. For patients with community-acquired infection this usually means culture of urine, sputum, a throat swab, stool, cerebrospinal fluid or any accessible serous fluid. Only serous fluid and CSF are reliably sterile. Other sites will demonstrate their normal bacterial flora unless selective media are used.

Urinary tract infection

Bacteriuria is predicted by the presence of cloudy urine, leucocytes or nitrites in the urine on dip stick examination. Nitrites may not be detectable if the organism does not possess the enzyme nitrate reductase e.g. *Staphylococcus* sp, *Enterococcus* sp, *Pseudomonas* sp, or if there is a lack of dietary nitrate or the patient is on diuretics.[24] Bacteruria however is common in asymptomatic elderly people. It is estimated that 20% of women and 2-3% of men of any age greater than 65 years of age and 23-50% of women and 20% of men greater than the age of 80 years have bacteriuria.[25] Hence, in a patient with sepsis and bacteruria, and without symptoms of urinary tract infection, other sources of infection should be considered. In our experience urinary infections are over-diagnosed, and this results in inappropriate and prolonged courses of antibiotics.

TABLE 4
Aetiology of Bacteraemia in the UK.[22]

Community-acquired		Hospital-acquired	
E. coli	25%	E. coli	25%
S. pneumoniae	22%	*Staph aureus*	19%
Staph aureus	10%	*Pseudomonas spp*	9%
'Viridans' *streptococci*	10%	*Klebsiella spp*	9%
Anaerobes	4%	Coagulas-negative *Staph*	7%
Klebsiella spp	3%	*Proteus mirabilis*	6%
Proteus mirabilis	3%	Anaerobes	5%
Other organisms	17%	Other enterobacteria	5%
		Other organisms	20%

Pneumonia and empyema

The main stay of diagnosis of respiratory tract infections is clinical examination and chest radiography. The radiograph is an essential investigation to differentiate pneumonia from other causes of respiratory tract infection and will determine antibiotic choice.[26] However hard one looks for pathogens in respiratory tract infections, the aetiology will remain unidentified in about 30% of patients. Sputum culture is useful when a good quality specimen is obtained and if there is a prolific growth of *Pneumococcus* or *Staphylococcus* in the presence of pus cells; a mixed growth usually reflects the normal oral flora. Ziehl Neelsen stain for acid and alcohol fast bacilli and culture for tuberculosis should be considered in all patients with respiratory symptoms and systemic upset that have lasted more than two weeks, particularly if the patient comes from a high-risk group. It should be remembered that there is a spectrum of disease and some patients presenting late may be *in extremis* with signs suggestive of severe pneumonia. Atypical infections such as *Chlamydia pneumoniae*, *Chlamydia psittaci*, *Mycoplasma pneumoniae*, *Legionella pneumoniae* and *Coxiella burnetti* are most reliably diagnosed by serology or in the case of *Legionella*, with antigen detection in the urine which will detect most serotype I infections.

Patients with a significant collection of pleural fluid

should have diagnostic thoracocentesis. Empyema may be difficult to diagnose in the absence of a positive Gram stain or culture. In these circumstances pH <7.1, lactate dehydrogenase >1000u/l and leucocytes >50,000 x 10^9/l and pleural glucose <40mg/dl will reliably diagnose an empyema.[27]

Gastrointestinal infections

Gastrointestinal infections usually do not present with sepsis although bacteraemia with some *Salmonella* species occur in <5 % of cases and there is a small risk of vascular infection. Achlorhydria, immunosuppression and inflammatory bowel disease predict risk of systemic disease; thus these patients should be treated empirically with a quinolone antibiotic.[28] Infections with *Campylobacter* are usually self-limiting but there are often systemic signs of infection and patients rarely become bacteraemic. Three stool cultures should be sent to give the best sensitivity.

In patients who develop infective diarrhoea in hospital or following antibiotic use in the community the cause is most often *Clostridium difficile*. This is now the commonest cause of bacterial diarrhoea in the elderly in the UK. It is diagnosed most readily by toxin detection. Two stool samples will detect 91% of cases.[29]

Stool culture in hospitalised patients is rarely useful although electron microscopy may be useful in hospital outbreaks where small round structured virus or rota virus may be implicated.

Infective endocarditis

The Duke criteria[30] have given consistency to the diagnosis of endocarditis and have proven to be more sensitive than previously used criteria.[31] A definite diagnosis of endocarditis requires either pathological proof following surgery, or two major criteria or one major and three minor or five minor criteria. Major criteria are at least two positive blood cultures of a typical organism or persistently positive blood cultures >12 hours apart of another organism and clear-cut evidence of endocardial involvement (oscillating mass, abscess, partial dehiscence of a prosthetic valve or a new regurgitant murmur). Minor criteria are a predisposing heart condition or a history of intravenous drug misuse, temperature >38°C, vascular phenomena, immunological phenomena, consistent but not definite echocardiographic findings (e.g. valve thickening) and one positive blood culture or serological evidence of an associated infection. If there is a firm alternative diagnosis or resolution of the manifestations within four days of appropriate antibiotic therapy then the diagnosis is rejected. It should be remembered that a normal trans-thoracic echocardiogram does not exclude vegetations. In *Staphylococcus aureus* endocarditis only 34% of patients with definite endocarditis have vegetations demonstrated by trans-thoracic echocardiography.[32] Therefore if the diagnosis is suspected and the trans-thoracic 'echo' is negative transoesophageal 'echo' should be performed.

Soft tissue infections

Soft tissue infections are usually self-evident when acquired in the community or following surgery. However, in patients with sepsis in whom the source is not immediately obvious careful attention should be paid to pressure areas and the perineum. Early necrotising fasciitis is characterised by mild to moderate soft tissue inflammation and induration, with pain out of proportion to the skin's appearance. Patients are also systemically unwell, usually with hypotension secondary to exo-toxin production. Such patients require urgent surgical assessment, prompt antibiotic therapy and fluid resuscitation.[33]

Bacterial meningitis

Bacterial meningitis should be considered in all patients with fever and headache unless there is another obvious source of infection such as bacterial pharyngitis. There is a growing reluctance to perform lumbar puncture because of fear of coning. This is however an extremely rare event and may be attributable to other factors such as the host immunological response to microbe lysis following antibiotic administration. It is not necessary to perform lumbar puncture if the diagnosis is clinically obvious e.g. as in meningococcal infection with purpuric rash, and this investigation is contra-indicated if severe sepsis is present or there is evidence of raised intra-cranial pressure. It is however important for patients to have blood cultures prior to antibiotic treatment in hospital if possible. Even if antibiotics have been administered prior to culture, growth of pathogenic organisms may still occur. Other techniques such as PCR for meningococcus in whole blood or capsular antibody tests can improve diagnostic sensitivity and should be available in most centres, at least through reference laboratories.[34]

Septic arthritis

Septic arthritis in the native joint is most commonly caused by *Staph aureus*, *Strep pneumoniae* and *Strep pyogenes*. In the United States *Neisseria gonorrhoea* is more common. Clinical signs of the systemic inflammatory response do not differentiate septic arthritis from other inflammatory arthropathies so synovial fluid must be examined promptly and blood cultures performed. Septic arthritis usually yields a white cell count of >50,000 x 10^9/l cells/mm^3 although counts may be lower and overlap with inflammatory arthropathies.[35] Gram stain should be performed but may be negative in one-quarter of patients with *Staphylococcal* infections. Polarised microscopy should also be used to detect crystal-induced arthropathy. Culture may be negative due to prior antibiotic use and inhibitors present in pus. Protein and glucose estimations are often unhelpful because of overlap with inflammatory arthropathies but lactate dehydrogenase is usually elevated.[35] If investigations are equivocal it is often necessary to treat empirically.

Acute phase proteins

Other tests may be useful in assessing patients with suspected infection but are non-specific and usually are unhelpful in localising the site of infection. Acute-phase proteins such as complement, C-reactive protein (CRP), fibrinogen, haptoglobin, serum amyloid A and ferritin are produced by hepatocytes following stimulation by cytokines, in particular interleukin-6, and are increased in infection. An acute phase response, defined as a 25% increase or decrease in plasma concentration, is not specific for infection as it occurs in other conditions which produce a systemic inflammatory response.[36] Although the majority of acute phase proteins show an increase during an acute event some, such as albumin and transferrin, decrease. Other acute-phase phenomena such as anaemia and thrombocytosis are postulated to occur as a result of cytokine-mediated effects

on bone marrow. The erythrocyte sedimentation rate (ESR), which is no longer used in our hospital Trust, reflects the plasma concentration of fibrinogen but also the size, shape and number of red cells so is not as informative as the CRP. In our clinical practice the CRP is used to differentiate inflammatory from non-inflammatory conditions. In particular we find it a useful test for monitoring response of deep-seated infections (such as endocarditis) to therapy as it changes rapidly. Markedly elevated CRP concentrations (>100mg/l) usually suggest bacterial or fungal infections in the absence of other overt inflammatory conditions.[36] However in our experience some patients with serious bacterial infections may have moderately elevated or even normal CRP concentrations. The CRP can be useful in patients with Systemic Lupus Erythematosus (SLE). In those without acute serositis the CRP is raised in patients with bacterial infection but not as acute exacerbations of SLE. A low or undetectable CRP however is usually good evidence against bacterial sepsis.[36]

SEPSIS MANAGEMENT

General measures

Antibiotics must be delivered as soon as possible after an infective episode is suspected, and blood cultures or other quick relevant investigations have been performed. This has been shown to be of vital importance in meningococcal disease[18] and in pneumonia in the elderly.[17] It seems prudent to extrapolate such findings to all situations where sepsis occurs. Empiric antibiotic prescribing should also reflect the likely infecting organism(s) and local sensitivity patterns, and should also be guided by local policy. However, antibiotic therapy alone will not be sufficient to effect cure in all patients. Prompt supportive therapy with oxygen, intravenous fluids and circulatory support are essential elements in the management of the septic patient. Hydration is compromised due to poor intake, sweating, tachypnoea and diarrhoea which are frequent accompaniments of sepsis. In such patients intravenous crystalloid solutions (between two and four litres daily depending on age and hydration status) should be administered in addition to oral intake. Hypotension may result from hypovolaemia or vasodilatation due to circulating inflammatory mediators or impaired myocardial contractility. In such circumstances our usual practice is to administer immediately one or two units of colloid (Gelofusine or Haemaccel) intravenously and give further volume replacement as necessary with crystalloid. If patients are persistently hypotensive despite volume replacement (assessed clinically and by central venous pressure monitoring), an inotropic agent such as dopamine is commenced and the patient is transferred to an intensive care unit for more invasive monitoring and inotropic/vaso-active drug management. Most patients in such circumstances require four to six litres of fluid before they can be judged to be adequately hydrated.[37] Patients should be catheterised to monitor urine output. Oliguric, normotensive patients who are adequately filled may respond to a renal dose of dopamine but should be managed in at least a high dependency unit.

Oxygenation should be optimised in patients with sepsis. Demands are increased due to the catabolic state and delivery is reduced due to ventilation/perfusion mismatches and systemic circulatory changes. Adult Respiratory Distress Syndrome may develop and this is fatal without ventilation. High flow oxygen (60% or greater) is administered to patients with sepsis syndrome irrespective of the source of sepsis or the arterial blood oxygen concentration as this can change rapidly, particularly as patients become fatigued. Persistent tachypnoea despite high flow oxygen suggests the patient is at risk of respiratory arrest. Our policy is to identify these patients early and refer for intensive care support before arrest occurs.

Antibiotic prescribing

Patients share the same wards, nursing care, junior medical staff and, after admission to hospital, the same skin flora. Antibiotics are usually prescribed by the most junior and inexperienced member of the medical team, often with little guidance from their seniors and often with no responsibility for continuing care of the patient due to cross-cover arrangements. Once administered an antibiotic alters gut, skin and respiratory tract flora and the process of selection of antibiotic resistant species and opportunistic pathogens begins. Hence the effects of an antibiotic go well beyond the individual patient or the targeted micro-organism. It therefore seems to be common sense that there should be an attempt to unify and rationalise antibiotic prescribing as far as possible within the common environment of the hospital.

Within our Trust the management of bacteraemia and sepsis has traditionally been based on the use of a hospital antibiotic formulary, telephone-based consultation by Medical Microbiologists, advice from the ward pharmacist and (infrequent) solicited requests for infectious diseases (ID) consultation or (more frequently) 'curb side consultations'. These ID consultation requests are often too late in the course of the illness when complications have arisen because of failure of response to initial antibiotic therapy. Antibiotic formularies are often seen by clinicians as restrictive and whether they actually lead to an overall reduction in antibiotic prescribing cost has recently been questioned.[38] However controlling antibiotic use in conjunction with improved infection-control practices can influence the prevalence of resistant organisms in a hospital.[39]

Because of increasing concerns over unrestricted antibiotic prescribing and a steady increase in the prevalence of resistant micro-organisms, a number of initiatives have been undertaken to improve the management of infection in Dundee. It is appreciated that such initiatives are limited by available resources but recommend that hospitals consider a multi-disciplinary approach to antibiotic use utilising those who are involved in day-to-day infection management e.g. microbiology, infectious diseases, pharmacy and nursing.[40]

Initial management of sepsis

It is unlikely (and unnecessary) that all patients with suspected sepsis admitted to hospital are seen by a specialist in infection. Therefore, the provision of a sepsis protocol should be readily available for prescribers. This ensures optimal and consensus management for the patient first presenting with suspected sepsis and controls, to a degree, the use of expensive or 'high risk' antibiotics.

In Dundee the sepsis protocol (Figure 1) is designed for use by junior doctors who usually make initial decisions regarding management. It is issued to every doctor in the Trust in a pocket-sized laminated form and is also made available in poster form on all the relevant wards. It

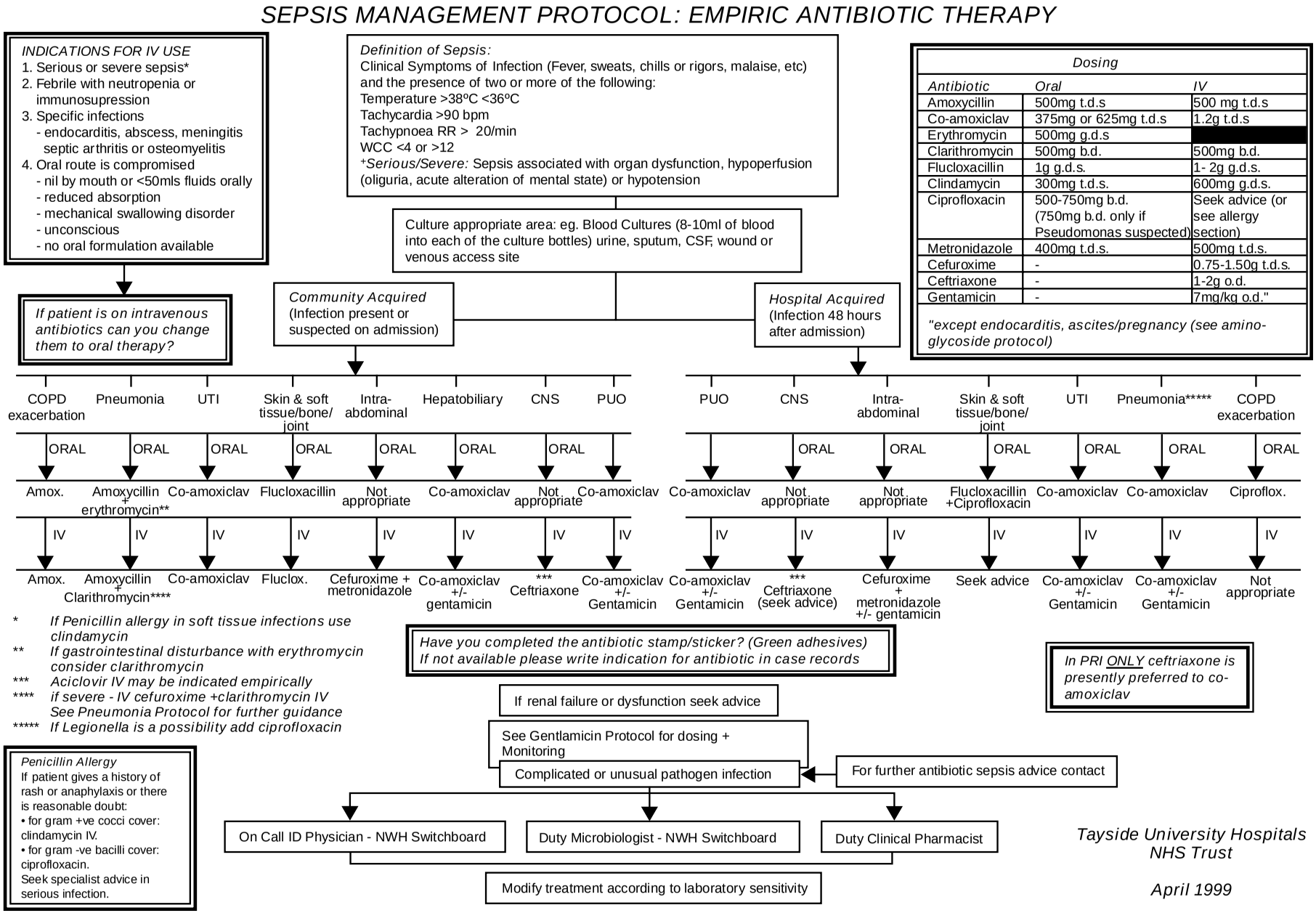

FIGURE 1
Tayside University Hospital sepsis protocol.

reinforces the importance of sepsis recognition by incorporating in it panels which outline the features of sepsis, highlight the importance of key investigations such as blood culture and emphasise the importance of source of infection (hospital- or community-acquired). The protocol deliberately limits empiric antibiotic prescribing to a small number of key drugs and gives the prescriber a best-guess antibiotic for most situations. The choice of antibiotic is deliberately restrictive but reflects the prevalence of common pathogens and trends in antibiotic susceptibility in our region. The emphasis is on the use of penicillin-based antibiotics adding gentamicin for improved Gram-negative coverage in severe infections. Cephalosporins are infrequently used first-line because of their association with *Clostridium difficile* infections[41] and emergence of nosocomial enteroccal infections.[7] At present glycopeptides (vancomycin and teicoplanin) are reserved for patients with proven MRSA infection or low risk Gram-positive infections managed outside the hospital.[42] Infections in patients with penicillin hypersensitivity are treated with clindamycin and/or ciprofloxacin which in our experience are well tolerated.

To ensure that new junior staff are aware of this protocol, it is presented to them during their orientation programme, it is included in their protocol book and is reinforced *ad hoc* by the ward pharmacist. The protocol is continuously monitored, audited and updated depending on changes in the epidemiology of infection in the Trust. The impact of such educational programmes on reducing total antibiotic expenditure have been shown elsewhere.[43]

Unsolicited consultation service for bacteraemia

A consultation between attending clinicians and an infection specialist, either an ID physician or clinical microbiologist, has many clinical, microbiological and economic advantages to the attending team, patient and hospital. These include significantly less inappropriate initial antibiotic treatment, better use of microbiology data, less persistence of infection as well as more easily defined financial advantages.[19, 44-48] In our hospital Trust an 'infection consultation service' (consisting of ID clinicians and medical microbiologists) was developed along the lines previously described at Northwick Park Hospital in London.[49] All patients from the Medical or Surgical Directorates who have positive blood cultures are visited within 24 hours by an ID physician and advice offered regarding management. It is of paramount importance that non-specialist clinicians co-operate with such developments and see them as being of benefit to the service and not as a restriction on their clinical freedom. In our experience, the interventions implemented in Dundee have been well received by all concerned and have led to some reduction in antibiotic prescribing costs as well as improvement in the quality of prescribing.[50]

Expensive parenteral antibiotics

Data from the USA reported a trend of increasing total antibiotic (old and new agents) consumption, and a similar high overall use of parenteral agents and of combination therapy.[51] Reports from our own hospital pharmacy confirm escalating costs due to antibiotic use, particularly in the Directorate of Medicine where parenteral antimicrobials account for a significant proportion of this cost.

Many ways can be considered to attempt to curb the use of expensive and broad spectrum parenteral antimicrobials. For example, an automatic stop order on prescriptions of certain agents or prescriptions limited by prior approval of a microbiologist, ID physician or a patient's consultant. In the UK approximately one-quarter of hospitals operate an automatic stop order programme, while nearly three-quarters have a restricted list requiring sanction by a senior or specialist member of staff.[52] The latter appears to be a particularly effective strategy when prior approval from an ID physician is required for certain antimicrobials and has been shown to significantly reduce expenditure and prevalence of antimicrobial resistance without compromising patient safety.[53] Agents such as intravenous ciprofloxacin, imipenem/meropenem, ceftazidime, cefotaxime, vancomycin, teicoplanin and amphotericin B are consistently amongst the most commonly, and often irrationally, prescribed agents. When these are given inappropriately they are primarily responsible for escalating antibiotic costs. Furthermore, *Clostridium difficile* diarrhoea, enterococcal and resistant Enterobacter bacteraemia (cephalosporins)[6,38,54] and other serious adverse effects such as CNS toxicity/seizures (imipenem-cilastatin) are also more common; overuse of any antibiotic may encourage the emergence of other resistant strains. Safer, cheaper and equally effective options are often available, allowing us to reserve these antibiotics for special cases or when there is a clear-cut microbiological indication.

In Dundee our 'alert antibiotic scheme' has been successful. Alert antibiotics are identified by the ward pharmacist during his/her daily ward visits. Should their use be outside the indications agreed, the attending clinician will be alerted of this and advised to discuss its continual use with the on-call ID physician or microbiologist. The list of antibiotics and their indications have been agreed by all members of the antibiotic subcommittee which consists of a multi-disciplinary team, and would also have to be agreed and supported by the Drug and Therapeutics Committee, Clinical Directors and members of Trust Executive Group. The role of the pharmacist/microbiologists or ID physician should purely be advisory. Regular audit of use of these antibiotics is proposed so that each individual clinician will be presented information on their own prescribing of these antibiotics, particularly outside the indications outlined.

Switch therapy programme

In our own hospital between 1992 and 1993 there was a 38% increase in total antibiotic expenditure of which 86% was due to increase in parenteral antibiotic usage. Many patients are often kept in hospital purely for the purpose of completing the course of intravenous therapy although the wide variations in length of stay are probably due to multiple factors including disease severity, patient characteristics and the differing practice patterns of various institututions.[55] Secondly, even after changing to oral therapy, patients are kept in hospital for observational purposes when early hospital discharge would have been safe and cost-effective.[56,57] In the current economic climate, clinicians are increasingly being asked not only to consider efficacy of antibiotic treatment but also administer it in a cost-effective manner. Therefore, one of the increasingly popular options is the identification of those hospitalised patients who are suitable for early conversion from parenteral to oral antibiotic therapy with subsequent hospital discharge. The latter strategy of switch or sequential therapy is the

practice of early transition from parenteral to oral therapy with the end-result of reducing the length of hospital stay and overall cost of treatment without compromising clinical outcome.[58]

Audits in our own hospital Trust have shown delays in switch due to a reluctance by junior staff to change to oral therapy before the next consultant ward round or at weekends. Such delays lead to unnecessary work load, financial expenditure and put the patient at risk of intravascular device-related infection. Recently an intravenous to oral switch therapy programme has been introduced onto selected wards to try and improve this situation.[40]

CONCLUSIONS

With careful consideration of clinical signs and prudent use of simple investigations it is possible to diagnose and assess the severity of bacterial infection in hospital. The combination of infection management services such as sepsis protocols, bacteraemia consultation services, alert antibiotic schemes and switch therapy programmes are designed to guide and rationalise antibiotic therapy for the individual and limit development of antimicrobial resistance and adverse effects of antibiotic administration. Regular monitoring of such schemes and linkage to clinical and microbiological outcome and feed-back to prescribers is essential. These strategies should lead to better antibiotic prescribing and in conjunction with infection-control measures should help the control of emerging antibiotic resistance within hospitals.

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