Empirical choice of antibiotic therapy in sepsis

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The management of sepsis is a recurring challenge in hospital practice. Sepsis affects all age groups. In adult medicine it is increasing in absolute numbers affected as well as in complexity and severity, since those age 65 years and over are the predominant age group affected. Furthermore, while bacterial infections are the leading cause of serious sepsis, other microorganisms including viruses, fungi and protozoa should be kept in mind. For example, candidaemia may complicate intensive care management, and malaria or viral haemorrhagic fevers should always be considered in the febrile returning traveller. In the case of bacterial sepsis, the changing and often unpredictable susceptibility to antibiotics of many common hospital and community pathogens further complicates disease management. Poor outcome has been linked in many studies to inappropriate choice of the initial antimicrobial regimen.

Sepsis is rarely a diagnosis in isolation. Defining a source and the circumstances of the syndrome is crucial to the initial assessment and in identifying the likely microbiological cause. These factors in turn dictate the choice and regimen of initial empirical antibiotic therapy since few presentations are diagnostic for a specific microorganism.

Patient assessment

The basis for effective antibiotic prescribing includes a thorough review of the clinical history, supplemented by information from household members and other contacts, as well as general practitioner and hospital records, as appropriate. Recent travel and animal exposure should be determined, and also the possibility of food-associated disease. Current medication should be noted.

The presence of specific risk factors for sepsis should be sought (Table 1). These include:

- pre-existing disease
- medical interventions, including immunomodulating and cytotoxic therapy
- lifestyle issues.

Key Points

- The microbial aetiology of the sepsis syndrome is diverse but bacterial pathogens predominate
- The bacterial aetiology usually reflects the clinical source of sepsis
- Hospital-acquired pathogens may be multiresistant and include methicillin-resistant Staphylococcus aureus, Klebsiella and Pseudomonas spp.
- Investigations should include cultures of blood and other infected body fluids, as clinically indicated
- Empirical antibiotic therapy should be tailored to the source of the infection
- The pathophysiological response to sepsis can enhance drug toxicity
- Regular review and adjustment of management are essential in the septic patient
In the case of hospitalised patients, recent surgery, invasive procedures, infected infusion sites or pressure areas may be the portal of entry, while intubation, impaired consciousness and pharyngeal dysfunction may lead to hospital-acquired or aspiration pneumonia. In addition, the ward or unit in which the patient develops sepsis can be important. Endemic hospital pathogens, such as methicillin-resistant *Staphylococcus aureus* and multi-resistant Gram-negative bacilli (*Klebsiella, Pseudomonas and Acinetobacter* spp.) are widespread, while vancomycin-resistant

### Table 1. Risk of factors for sepsis.

**Disease**
- Immunodeficiency
- congenital
- hyposplenism
- HIV infection
- Immunosuppressive/cytotoxic therapy
- Malignancy
- Diabetes mellitus
- Cardiac failure (severe)
- COPD
- Neutropenia <0.5 x 10⁹/l
- Chronic renal failure (especially dialysis)
- Trauma
- Burn wounds
- Epilepsy
- CVA

**Care associated**
- Nursing home
- Mechanical ventilation
- Dialysis procedures
- CSF shunts
- Intravascular lines
- Bladder catheter
- Pressure sores

**Lifestyle**
- IVDA
- Ethanol dependency

COPD = chronic obstructive pulmonary disease; CSF = cerebrospinal fluid; CVA = cerebro-vascular accident; IVDA = intravenous drug abuse.

### Table 2. Pathogens most commonly associated with site-specific diseases or syndromes.

| Site                  | Disease/Syndrome                      | Common pathogens                                      |
|-----------------------|---------------------------------------|-------------------------------------------------------|
| Central nervous system| Meningitis                            | *Streptococcus pneumoniae*                             |
|                       |                                       | *Neisseria meningitidis viruses*                       |
|                       |                                       | *Listeria monocytogenes*                               |
|                       |                                       | *Herpes simplex*                                       |
|                       |                                       | *Micro-aerophilic streptococci*                         |
|                       |                                       | *Anaerobic bacteria*                                   |
|                       | Brain abscess                         | *Gram-negative enteric bacteria*                       |
|                       |                                       | *Staphylococcus aureus*                                |
| Upper respiratory tract| Tonsillopharyngitis                   | *Streptococcus pyogenes*                               |
|                       | Quinsy                               | *S. pyogenes*                                          |
|                       | Epiglottitis                          | *Anaerobic bacteria*                                   |
|                       | Ludwig’s angina                       | *Haemophilus influenzae*                                |
|                       |                                       | *Anaerobic + Gram-negative enteric bacteria*            |
| Lower respiratory tract| Pneumonia                             | *S. pneumoniae*                                        |
|                       | • community-acquired                  | *Mycoplasma pneumoniae*                                |
|                       | • hospital-acquired                   | *Legionella pneumophila*                               |
|                       | • aspiration                          | *Gram-negative enteric bacteria*                       |
|                       | Lung abscess                          | *S. aureus*                                            |
|                       |                                       | *Anaerobic, micro-aerophilic & anaerobic bacteria*      |
|                       | Acute infective exacerbations         | *Gram-negative enteric bacteria*                       |
|                       | of chronic bronchitis                 | *H. influenzae*                                        |
|                       | Cystic fibrosis                       | *S. pneumoniae*                                        |
|                       |                                       | *M. catarrhalis*                                       |
|                       |                                       | *Pseudomonas aeruginosa*                               |
|                       |                                       | *Burkholderia cepacia*                                 |
|                       |                                       | *S. aureus*                                            |
| Skin & skin structure | Erysipelas                            | *S. pyogenes*                                          |
|                       | Cellulitis                            | *S. pyogenes*                                          |
|                       | Necrotising fasciitis                 | *S. pyogenes*                                          |
|                       | Gas gangrene                          | *Anaerobic bacteria*                                   |
|                       |                                       | *Clostridium perfringens*                              |
| Hepatobiliary system  | Cholecystitis/cholangitis             | *Gram-negative enteric pathogens*                      |
|                       | Liver abscess                         | enterococci                                            |
|                       |                                       | *Micro-aerophilic streptococci*                         |
|                       |                                       | *Anaerobic bacteria*                                   |
| Intra-abdominal sepsis| Peritonitis                           | *Gram-negative enteric bacteria*                       |
|                       | Diverticulitis Abscess                | *S. aureus*                                            |
| Genitourinary         | Ovarian abscess                       | *Neisseria gonorrhoeae*                                |
|                       | Pelvic abscess                        | *Anaerobic bacteria*                                   |
|                       | Disseminated gonococcaemia           | *Anaerobic bacteria*                                   |
|                       |                                       | *Gram-negative enteric bacteria*                       |
|                       |                                       | *N. gonorrhoeae*                                       |
| Urinary tract         | Cystitis (uncomplicated)              | *Escherichia coli*                                     |
|                       |                                       | enterococci                                            |
|                       |                                       | *Staphylococci*                                        |
|                       |                                       | *E. coli & other Gram-negative enteric pathogens*      |
|                       |                                       | *P. aeruginosa*                                        |
|                       |                                       | *MRSA*                                                 |
|                       | Cystitis (complicated)                | *Gram-negative enteric bacteria*                       |
|                       |                                       | *Gram-negative enteric bacteria*                       |
|                       |                                       | *S. aureus*                                            |
| Bone and joint        | Osteomyelitis                         | *S. aureus*                                            |
|                       | Septic arthritis                     | *Salmonella*                                           |
|                       | Bursitis                             | *S. aureus*                                            |

MRSA = methicillin-resistant *Staphylococcus aureus*. 

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enterococci are of increasing importance in some hospitals (notably in renal and haematology units). The susceptibility of these pathogens to antibiotics is often unpredictable, with limited options for management.

**Presenting features and associated pathogens**

The clinical features usually indicate a probable site or source of infection in the septic patient. Defining a clinical diagnosis permits prediction of the most likely responsible pathogens. Table 2 summarises the common presenting syndromes and their associated microbiological causes (it should not be considered exhaustive). Appropriate laboratory and radiographic investigations should be promptly organised. For microbiological assessment, blood cultures are important as is culture of other body fluids relevant to the presumptive diagnosis. Such investigations should not delay management of the critically ill patient but, when positive, can have an important bearing on subsequent patient management, as well as permitting a more accurate prognosis. Occasionally, they lead to public health action or indicate the need for hospital infection control.

**Choice of regimen**

The selection of initial empirical therapy is governed not only by the antimicrobial spectrum but also by the pharmacokinetic profile to ensure sufficient drug is delivered to the site of the infection.

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**Table 3. Choice of agent for initial empirical parenteral therapy of the site- and diagnostic-specific sepsis occurring in hospitalised adults.**

| Disease                        | Preferred                  | Alternative               |
|--------------------------------|----------------------------|---------------------------|
| Meningitis                     | ceftriaxone                | meropenem                 |
| Meningoencephalitis            | aciclovir                  | chloramphenicol           |
| • viral (Herpes simplex)       | ampicillin                 | co-trimoxazole            |
| • listeria                     | ± gentamicin               | cefuroxime                |
| Tonsillopharyngitis            | penicillin G               | cefuroxime + metronidazole|
| Quinsy                         | penicillin G + metronidazole| ciprofloxacin             |
| Epiglottitis                   | cefotaxime                 | ciprofloxacin + clindamycin|
| Ludwig's angina                | cefuroxime + metronidazole |                          |
| Pneumonia                      |                            |                           |
| • community-acquired (severe)  | co-amoxiclav, cefuroxime, or cefotaxime + erythromycin or clarithromycin | meropenem ± clarithromycin|
| • hospital-acquired (severe)   | cefotaxime, ceftriaxone ± vancomycin (if MRSA suspected) | meropenem                 |
| • aspiration                   | penicillin + metronidazole + fluoroquinolone* | clindamycin + gentamicin |
| Lung abscess                   | flucloxacillin + fluoroquinolone* | clindamycin + gentamicin |
| Acute infective exacerbation of chronic bronchitis | penicillin G + levofloxacin | cefuroxime, cefotaxime or co-amoxiclav |
| Cystic fibrosis                | cefazidime ± flucloxacillin | piperacillin/tazobactam |
| Erysipelas                     | penicillin G               | erythromycin or clindamycin|
| Cellulitis                     | flucloxacillin             | clindamycin               |
| Necrotising fasciitis          | flucloxacillin + metronidazole + ciprofloxacin | clindamycin + gentamicin |
| Gas gangrene                   | penicillin G               | chloramphenicol           |
| Cholecystitis/cholangitis      | ampicillin + gentamicin    | fluoroquinolone* + metronidazole |
| Liver abscess                  | penicillin G + metronidazole + gentamicin | clindamycin + fluoroquinolone* |
| Peritonitis                    | ampicillin + gentamicin + metronidazole | meropenem or fluoroquinolone* + metronidazole |
| Diverticulitis                 |                            |                           |
| Intra-abdominal abscess (includes pelvic abscess) |                            |                           |
| Ovarian abscess                | penicillin G + gentamicin + metronidazole | fluoroquinolone* + metronidazole |
| Acute pyelonephritis           | cefuroxime                 | fluoroquinolone*          |
| Perinephric abscess            | cefuroxime                 | fluoxacillin + gentamicin |
| Osteomyelitis                  | flucloxacillin ± gentamicin| clindamycin ± ciprofloxacin|
| Septic arthritis               | flucloxacillin ± fusidic acid | clindamycin               |
| Bursitis (septic)              | flucloxacillin             | clindamycin               |

* fluoroquinolone: ciprofloxacin or levofloxacin. MRSA = methicillin-resistant Staphylococcus aureus.
In selecting the regimen, due attention should be paid to any history of drug intolerance or hypersensitivity reactions. The potential for an increased risk of drug toxicity as a result of excretory organ failure or drug interactions should be carefully considered in the septic patient.

Assessment of severity is important in relation to prognosis and also influences management. This has been particularly well defined in relation to community-acquired pneumonia where assessment of severity determines the initial choice of therapy and route of administration. However, this degree of evidence-based precision is lacking for many other diagnoses. The pre-morbid state is also important in determining prognosis. Sepsis complicating underlying rapidly fatal, ultimately fatal and non-fatal disease has readily distinguishable survival rates.

Table 4. Initial empirical therapy: adverse reactions and drug interactions.

| Drug               | Adverse reactions                                      | Drug Interactions          |
|--------------------|--------------------------------------------------------|----------------------------|
| Aciclovir          | rashes                                                 | mycophenolate mofetil      |
|                    | gastrointestinal intolerance                           |                            |
|                    | hepatoxicity                                           | probenecid                 |
|                    | nephrotoxicity                                         |                            |
|                    | confusion                                              |                            |
|                    | tremors                                                |                            |
|                    | seizures                                               |                            |
| Cephalosporins     | rash                                                   | anticoagulants             |
|                    | diarrhoea                                              | oral contraceptive pill    |
|                    | *Clostridium difficile* enteropathy                    |                            |
| Chloramphenicol    | marrow toxicity (includes aplastic anaemia)            | anticoagulants             |
|                    | neutropathies                                          | anticonvulsant             |
|                    |                                                        | sulphonylurea              |
| Ciprofloxacin      | gastrointestinal                                       | antacids                   |
|                    | hepatitis                                              |                            |
|                    | nephritis                                              | anticoagulants             |
|                    | rashes                                                 | cyclosporin                |
|                    | erythema nodosum                                       | NSAI ds                    |
|                    | tenosynovitis                                          | oral iron                  |
| Clarithromycin     | gastrointestinal intolerance                           | amiodarone                 |
|                    | hepatoxicity                                           | anticonvulsants            |
|                    | Stevens-Johnson syndrome                               | antiretrovirals             |
|                    |                                                         | cyclosporin                |
|                    |                                                         | disopyramide               |
|                    |                                                         | midazolam                  |
|                    |                                                         | pimozone                   |
|                    |                                                         | reboxetine                 |
|                    |                                                         | rifabutin                  |
| Clindamycin        | rash                                                   | muscle relaxants           |
|                    | diarrhoea                                              |                            |
|                    | hepatoxicity                                           |                            |
|                    | *Clostridium difficile* enteropathy                    |                            |
| Co-trimoxazole     | hypersensitivity reactions                             | amiodarone                 |
|                    | Stevens-Johnson syndrome                               | anticonvulsants            |
|                    | marrow toxicity                                        | cyclosporin                |
|                    | crystalluria                                           | methotrexate               |
|                    | nephritis                                              | sulphonylureas             |
| Fusidic acid       | gastrointestinal intolerance                           | amphotericin               |
|                    | hepatoxicity                                           | anticoagulants             |
|                    | rashes                                                 | cisplatin                  |
| Gentamicin         | audiotoxicity                                          |                            |
|                    | vestibulotoxicity                                      |                            |
|                    | nephrotoxicity                                         |                            |
| Metronidazole      | gastrointestinal intolerance                           | alcohol                    |
|                    | rashes                                                 | anticoagulants             |
|                    | drowsiness                                             | anticonvulsants            |
|                    | ataxia                                                 | cimetidine                 |
|                    | seizures                                               | disulfiram                 |
|                    |                                                         | lithium                    |
| Penicillin         | hypersensitivity reactions                             | anticoagulants             |
|                    | gastrointestinal intolerance                           | excretion of methotrexate   |
|                    | hepatoxicity                                           | oral contraceptive pill    |
|                    | marrow toxicity                                        |                            |
|                    | *Clostridium difficile* enteropathy                    |                            |
| Vancomycin         | nephrotoxicity                                         | aminoglycosides            |
|                    | rashes                                                 | loop diuretics             |
|                    | 'red man syndrome'                                     |                            |

NSAID = non-steroidal anti-inflammatory drug.

Recommendations for management

The recommendations for therapy (Table 3) should be used as a guide to management, recognising that they are based on knowledge of the microbiological spectrum, the pharmacokinetic and pharmacodynamic characteristics of the agent(s) under normal conditions of use, as well as on evidence for efficacy and safety. The evidence base may not always be robust, but custom and practice continue to support their use. Alternative regimens may perform equally effectively, and may be preferred where local microbiological patterns of disease dictate.

Intravenous administration is generally preferred and results in rapid therapeutic concentrations at the site of the infection. In particular, it avoids the vagaries of gastrointestinal absorption which may be compromised in severe sepsis. This route is mandatory in managing life-threatening infections such as bacterial meningitis, infective endocarditis and sepsis complicating profound neutropenia. Oral regimens may be considered in those with mild to moderate sepsis, provided that there are
no contraindications to their use and that the patients are reviewed regularly.

Safety

The pathophysiological response to sepsis affects many metabolic pathways, and when severe can result in multiple organ failure. The haemodynamic consequences of sepsis frequently affect drug absorption and distribution. Likewise, excretory routes can be compromised as a consequence of impaired tissue perfusion. Choice of therapy and dose adjustment may become necessary in the presence of altered renal function or hepatic insufficiency. Table 4 identifies some of the more important safety considerations for the agents recommended for empirical antibiotic therapy. Many seriously ill patients will be receiving multiple drugs, so it is important to be alert to the possibility of drug interactions.

Subsequent management

Sepsis is a dynamic process which dictates that the initial assessment and management of the septic patient, including the choice of empirical antibacterial therapy, should be regularly reviewed. Not only may the clinical features evolve, but the results of radiological, laboratory (including microbiological) tests may suggest the need for a reassessment of the diagnosis and management plan.

The results of stained smears of purulent material should be sought, while positive cultures of blood, cerebrospinal fluid, urine and other normally sterile body sites can provide invaluable information in defining the diagnosis and prompting a revision of antibiotic therapy.

In the absence of clinical improvement, it is important to review the possible causes of treatment failure. Table 5 summarises some of the more common considerations.

Conclusion

The importance of severe sepsis lies in its relative frequency and high mortality. Approximately 20% of patients with bacteraemic sepsis will develop septic shock, of whom approximately half will die. This mortality rate rises with the development of complications, such as adult respiratory distress syndrome or multiple organ failure. For these reasons, the prompt diagnosis and management of sepsis, including the choice of antibiotic therapy, can be life saving.

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Table 5. Sepsis syndrome: some causes of failure of initial empirical antibiotic therapy.

- Abscess requiring drainage
- Medical device-associated infections (IV line, prosthetic implant)
- Metastatic sepsis (eg septic arthritis, meningitis, endocarditis)
- Polymicrobial infection
- Less common infection (eg tuberculosis, aspergillosis, candidaemia, CMV)
- Incorrect choice of therapy
- Drug fever
- Non-microbial aetiology (eg vasculitis, metastatic malignancy, Behçet syndrome)

CMV = cytomegalovirus; IV = intravenous.