

Guidelines for the management of hospital-acquired pneumonia in the UK: Report of the Working Party on Hospital-Acquired Pneumonia of the British Society for Antimicrobial Chemotherapy

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These evidence-based guidelines have been produced after a systematic literature review of a range of issues involving prevention, diagnosis and treatment of hospital-acquired pneumonia (HAP). Prevention is structured into sections addressing general issues, equipment, patient procedures and the environment, whereas in treatment, the structure addresses the use of antimicrobials in prevention and treatment, adjunctive therapies and the application of clinical protocols. The sections dealing with diagnosis are presented against the clinical, radiological and microbiological diagnosis of HAP. Recommendations are also made upon the role of invasive sampling and quantitative microbiology of respiratory secretions in directing antibiotic therapy in HAP/ventilator-associated pneumonia.

Keywords: hospital-acquired pneumonia, healthcare-associated pneumonia, evidence-based guidelines, prevention, diagnosis, antimicrobial treatment

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1. Introduction

Hospital-acquired pneumonia (HAP) is a respiratory infection developing more than 48 h after hospital admission. HAP affects 0.5% to 1.0% of inpatients and is the most common healthcare-associated infection (HCAI) contributing to death.¹ It is estimated to increase hospital stay by 7–9 days.² In a proportion of patients, HAP is associated with mechanical ventilation, in which case it is termed ventilator-associated pneumonia (VAP). In patients with VAP, there is a 24% to 50% mortality rate, which increases to 76% if infection is caused by multidrug-resistant pathogens.³ VAP accounts for up to 25% of all intensive care unit (ICU) infections with the risk being highest during early ICU stay when it is estimated to be 3%/day during the first 5 days of ventilation, followed by 2%/day up to day 10 of ventilation and thereafter 1%/day.⁴ These features of high incidence with significant morbidity and mortality consequences have driven considerable recent interest in the creation of HAP guidelines. Prevention of HAP is therefore not only desirable but also essential for providing cost-effective healthcare. The Department of Health (DH) in its ‘Saving Lives’ initiative has seven high-impact interventions that are part of the programme to reduce HCAI and one of these relates to the care of the ventilated patient.⁵

Although guidelines for HAP in the UK have not been previously published, a total of 10 international HAP guidelines have been released over the last 7 years.⁶ Of these, only one both used a systematic review of the literature approach and covered each of prevention, diagnosis and treatment.⁷ These American Thoracic Society guidelines, however, used a semi-qualitative approach to assessment and did not weigh fully both the strength and the quality of the evidence. Over half of the available guidelines are based on expert opinion and cover only one or two of the three

Table 1. Grades of recommendation¹¹

Grades of recommendation	
A	at least one meta-analysis, systematic review, or RCT rated 1 + +, ^a and directly applicable to the target population; <i>or</i> A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1 + +, ^a directly applicable to the target population, and demonstrating overall consistency of results
B	a body of evidence including studies rated as 2 + +, ^a directly applicable to the target population, and demonstrating overall consistency of results; <i>or</i> Extrapolated evidence from studies rated as 1 + + ^a or 1 + ^a
C	a body of evidence including studies rated as 2 + , ^a directly applicable to the target population and demonstrating overall consistency of results; <i>or</i> Extrapolated evidence from studies rated as 2 + + ^a
D	evidence level 3 ^a or 4 ^a ; <i>or</i> extrapolated evidence from studies level 2 + ^a
Good Practice Point (GPP)	
Recommended best practice based on the clinical experience of the HAP Working Party of the BSAC	

RCT, randomized controlled trial.

^aSee ref. 11 for definitions of evidence assessments.

relevant areas of consideration. Recently, a number of guidelines have been published relating to prevention of both VAP^{7,8} and the combination of non-ventilator-associated HAP and VAP.^{6,9,10} These have been produced in different ways with none employing a full systematic review approach that fully meets an appraised quality methodology.

The guidelines presented here were developed by a Working Party of the British Society of Antimicrobial Chemotherapy (BSAC). The overall guideline is divided into three sections dealing with prevention, diagnosis and treatment. In producing the guidelines, the Working Party adopted a systematic review approach using a formally evaluated quality assessment mechanism. The tool chosen was the guideline development process produced by the Scottish Intercollegiate Guideline Network (SIGN).¹¹ This methodology includes an explicit description of the level, definitions and volume of evidence, which is reviewed by a multidisciplinary development team. The product grades the recommendations according to the quality of supporting evidence with the output being subject to a final expert peer assessment prior to release (Table 1). The SIGN tool has been assessed against and meets the guideline quality requirements of the Appraisal of Guidelines Research and Evaluation instrument.¹¹

Literature searches were undertaken on Medline, Embase, the Cochrane Database and professional and journal Internet sites. A definitive search string was developed for each question and if necessary for each subquestion. Strings were developed for Medline searches and amended accordingly for Embase searches. The searches were initially run in August 2002 with a final check in July 2005. The total number of search strings deployed was 31 for prevention, 7 for diagnosis and 15 for treatment. These yielded, respectively, 971, 1753 and 3868 citations for review with 350, 85 and 308 articles proceeding to formal full assessment. The scope of the guideline generally excludes

oral antiseptic treatments, severely immunocompromised patients, children <16 years old and patients with cystic fibrosis (CF). Consultation with stakeholders took place over an 8 week period through open access on the BSAC web site and through invited comments from relevant professional bodies and learned societies.

The guideline is divided into three main sections (prevention, diagnosis and treatment) to cover all relevant issues within the scope of the project. Prevention was divided into four sections to include the different modifiable aspects of patient care that can be used to help prevent against HAP. These include:

- General issues—staff education; use of clinical guidelines or protocols; screening patients and their environment, immunization strategies; hand hygiene and the use of personal protective equipment.
- Use of equipment—maintenance and sterilization or disinfection.
- Patient procedures—suctioning; non-invasive ventilation (NIV); method of endotracheal (ET) intubation; enteral feeding; prevention of aspiration; stress ulcer prophylaxis; breathing exercises, physiotherapy, incentive spirometry, positional strategies, the use of kinetic beds; use of red cell transfusions.
- Environmental issues—methods to reduce transmission of *Aspergillus* during building work; the use of antifungal prophylaxis; control of *Legionella* and cleanliness of the environment.

The work on diagnosis is divided into three sections that cover the main diagnostic approaches for HAP: clinical assessment, radiological investigation and microbiological investigation. Similarly, treatment is divided into five sections to include the different aspects of patient care. These cover both the use of antimicrobials in prevention and in treatment, the role of invasive sampling and quantitative microbiology of respiratory secretions in directing antibiotic therapy, the use of adjunctive therapies and the application of clinical protocols.

2. Prevention

2.1. General issues for the prevention of HAP

2.1.1. Role of staff education programmes

Only a limited number of studies addressed this issue. These included four cohort studies^{12–15} and one case–control study.¹⁶ Data from two cohort studies^{13,14} showed that education programmes are effective in reducing the incidence of VAP by 51% and 56%, respectively. A cohort study¹⁵ also showed that introducing protocols and education was effective in reducing VAP by 50%. One other cohort study¹² and a case–control study¹⁶ demonstrated that as part of a broad intervention, programmed education can be successful in controlling staff-to-staff or staff-to-patient outbreaks of primary respiratory pathogens, e.g. pertussis and respiratory syncytial virus. A cohort study showed that when a higher proportion of care was provided by qualified registered nursing staff, there was a lower incidence of HAP.¹⁷ Studies therefore consistently provide evidence that staff education programmes both in themselves and as part of an overall infection control programme reduce the incidence of VAP.

We recommend that hospital education programmes as part of an overall infection control strategy should form part of the risk reduction measures for HAP. Recommendation Grade B

Appropriate levels of experienced nursing staff should be involved in patient care to prevent HAP and education of staff on the measures that should be taken to prevent HAP should form part of their induction and continuing professional development. Recommendation Grade GPP

2.1.2. Role of clinical guidelines or protocols

Most published guidelines relate specifically to prevention of VAP rather than HAP. Two randomized controlled trials (RCTs) showed that care protocols in ICUs decrease the incidence of VAP, particularly in trauma patients.^{18,19} Two other RCTs, specifically on the use of weaning protocols for ventilated patients on ICU, found that the use of protocols by nurses and respiratory therapists resulted in reduced duration of mechanical ventilation, improved clinical outcome and reduced costs.^{20,21} Also the use of protocols for reducing sedation has been reported as being effective in shortening the duration of ventilation and ICU stay.^{22,23} Although there were few papers, those identified provided good evidence that clinical guidelines reduced the incidence of VAP.^{18–24} As there is no direct evidence that guidelines affect the incidence of HAP outside of ICUs, no recommendation can be made in respect of the value of clinical guideline implementation in this scenario.

We recommend that care protocols and guidelines for weaning and sedation should be developed and actively followed in the critical care setting to reduce the incidence of VAP. Recommendation Grade A

In order to reduce the incidence of HAP, adherence to clinical guidelines should be monitored to ensure compliance. Recommendation Grade GPP

2.1.3. Role of screening of patients or their environment to prevent HAP

There are no studies that examined the benefit of routine surveillance for HAP organisms in patients or their environment, in preventing HAP, and so no recommendation can be made on this topic. Future research is recommended in order to assess whether taking routine screening samples from patients helps to reduce the incidence of HAP or assists in targeting treatment through the early recognition of organisms causing HAP. Work is also needed to assess whether routine screening of the environment for organisms causing HAP reduces the incidence of HAP due to multiresistant Gram-negative bacteria, e.g. *Pseudomonas aeruginosa* or *Acinetobacter* spp.

We recommend that limited and targeted surveillance of organisms causing pneumonia in ICU patients should be carried out to identify cross-infection or outbreaks and other infection control problems, e.g. a single case of hospital-acquired *Legionella* infection.²⁵ This type of surveillance is also helpful in providing feedback to assist clinicians in empirical antibiotic selection and on the incidence and susceptibility of organisms causing VAP.²⁶ Recommendation Grade GPP

2.1.4. Immunization to prevent HAP

Immunization relevant to the prevention of HAP includes, particularly, influenza and pneumococcal vaccines. Most published papers cover influenza (including influenza pneumonia), the

elderly and healthcare workers and mainly relate to outbreaks in nursing homes. A meta-analysis²⁷ reviewing this area included 20 observational studies of HAP in the elderly and there are also cohort studies^{28,29} and three RCTs.^{30–32}

Existing UK guidance³³ already highlights the importance of immunization against influenza and pneumococcal disease for high-risk adult and paediatric patients. Immunization of healthcare workers involved with at-risk patients is also recommended. However, there is no direct evidence that influenza immunization of healthcare workers or patients will directly reduce the incidence of HAP, although one study²⁸ found evidence to suggest that influenza immunization prevents pneumonia in elderly patients. The same study reported that a failure to immunize healthcare workers against influenza was associated with an increased mortality from ‘influenza like illness’ in elderly patients. There is also no direct evidence that pneumococcal immunization of healthcare workers or patients reduces the incidence of HAP.

We recommend that the use of influenza immunization in healthcare workers and patients and pneumococcal immunization in elderly and at-risk groups should be encouraged. Recommendation Grade C

In line with the recommendations of the Joint Committee on Vaccination and Immunization,³³ influenza immunizations should be actively encouraged in at-risk patients and healthcare workers. Recommendation Grade GPP

2.1.5. Importance of hand hygiene in preventing HAP

A number of studies have assessed the effects of hand hygiene on staff-to-patient and staff-to-equipment transfer of bacteria. There is good evidence that an inverse relationship exists between high standards of hand hygiene and the incidence of HCAI, but there is no good evidence of a direct relationship with the prevention of HAP.^{34–38} Hand hygiene is effective in reducing HCAI and the *epic* Project evidence-based guidelines for the prevention of HCAI recommend implementation of a hand hygiene policy.³⁹

We recommend that hand hygiene guidelines are available as part of evidence-based processes for preventing HCAI and that these should be followed. Hand hygiene practices should be incorporated into clinical guidelines for the prevention of HAP and performance audits of these should be carried out to demonstrate and maintain high levels of practice. Recommendation Grade GPP

With a view to reducing the incidence of HAP, staff hand hygiene should form part of routine care with hands being decontaminated immediately before and after every episode of direct patient contact and after any activity or contact that potentially results in hands becoming contaminated. Hand decontamination after glove removal should be performed. Recommendation Grade GPP

2.1.6. Role of personal protective equipment

There is an absence of evidence to address this issue. The studies available relate to HCAI and not directly to HAP. There are data showing that the appropriate use of Personal Protective Equipment (PPE) prevents the spread of microorganisms and HCAI,^{39,40} which might potentially reduce the incidence of HAP. It is essential that the choice of PPE is appropriate to the risk of infection, e.g. simple surgical masks are inadequate in

protecting against tuberculosis and some respiratory viruses.⁴¹ Appropriate equipment needs to be readily available and the necessary training given in its use. National health and safety at work requirements such as PPE regulations^{42,43} and Control of Substances Hazardous to Health regulations⁴⁴ should be followed.

We recommend that the role of PPE in the prevention of HAP should involve local risk assessment with reference to national health and safety at work requirements, e.g. PPE Regulations^{42,43} and local infection control advice. Recommendation Grade D

We recommend high standards of hygiene including hand hygiene and PPE, as these will protect healthcare workers and patients against HCAI from microorganisms including influenza and other viral respiratory pathogens. Recommendation Grade GPP

Gloves should be put on immediately before an episode of patient contact or treatment and removed as soon as the activity is completed and should be changed between caring for different patients or between different care/treatment activities for the same patient. Recommendation Grade GPP

Care needs to be taken in the use of PPE to prevent spreading infection between patients, e.g. gloves can contaminate hands if not removed correctly and hence the importance of hand decontamination after glove removal.⁴⁵ Recommendation Grade GPP

Personal respiratory protection is required in certain respiratory infections, e.g. multidrug-resistant tuberculosis, human coronavirus etc. or when patients who are severely immunocompromised are exposed to infection [e.g. not in a high efficiency particulate air (HEPA)-filtered environment]. In these instances, specialized respiratory protective equipment should be worn. Recommendation Grade GPP

National guidelines should be followed with regard to protection of staff against highly communicable infections, e.g. human coronavirus. Recommendation Grade GPP

Isolation of patients with multidrug-resistant infections including pneumonia should be performed alongside the use of PPE to prevent the spread of infection. Recommendation Grade GPP

2.2. Infection control issues related to the use of equipment—best methods of sterilization or disinfection of equipment and maintenance of instruments

2.2.1. Mechanical ventilators

In respect of HAP risk reduction, there is an absence of evidence about the best sterilization/disinfection/maintenance procedures for mechanical ventilators. The reuse of ‘single-use’ devices can affect their safety, performance and effectiveness, exposing patients and staff to unnecessary risk. It also carries legal implications as anyone who reprocesses or reuses a device intended by the manufacturer for use on a single occasion bears full responsibility for that item’s safety and effectiveness, including to any organization to which the equipment is transferred.⁴⁶

We recommend that, in line with the Medical Device Agency guidance⁴⁶ on single-use medical devices, items designated for ‘single-use’ must not be reused under any circumstances. Recommendation Grade GPP

Equipment should be sterilized, disinfected and maintained according to the manufacturer’s instructions. Recommendation Grade GPP

2.2.2. Ventilator circuits

A systematic review which included four RCTs and seven observational studies found that changing the ventilator circuit less frequently than every 24 h reduced the risk of VAP.⁴⁷ Another systematic review⁴⁸ assessed three RCTs where one⁴⁹ was considered a higher quality trial than the other two.^{50,51} The review concluded that the frequency of ventilator circuit changes does not influence the incidence of VAP; that less frequent changes of ventilator circuits are not associated with harm and that more frequent changes are associated with increased cost. A further RCT found no difference in the rate of VAP in patients with ventilator circuits containing heat moisture exchangers (HMEs) where 48 h circuit changes were compared with no planned change.⁵² These studies were all conducted in ventilated patients where circuits were changed if there were signs of visible contamination or damage. Further research regarding safety and infection control criteria is required to determine the maximum length of time between ventilator tubing changes.

Provided they are otherwise changed if they become soiled or damaged, we recommend that ventilator circuits need not be changed before 7 days. Recommendation Grade A

New ventilator circuit tubing should be provided for each patient. Recommendation Grade B

In order to prevent contamination of the healthcare worker, facial protection should be used alongside PPE when closed breathing circuits are disconnected. This is especially important when dealing with patients with highly communicable infections, e.g. human coronavirus. Recommendation Grade GPP

To prevent VAP, breathing circuit condensate should be managed so that it does not drain towards the patient and it should be periodically drained and discarded.^{7,53} Recommendation Grade GPP

2.2.3. Heated humidifiers and HMEs

There are two meta-analyses^{47,54} and a systematic review⁴⁸ which have compared the use of heat humidifiers (HHs) and HMEs. One meta-analysis⁵⁴ covered all eight RCTs cited by the other papers that have examined the use of different humidifier types and their effect on the incidence of VAP.^{55–62} This meta-analysis concluded that in patients ventilated for >7 days, the use of HMEs is associated with a statistically significant reduction in the incidence of VAP when compared with HHs. Whereas concern was expressed in the earlier systematic review⁴⁸ about ET tube obstruction associated with HME use, this has not been confirmed in recent studies evaluating newer HMEs.⁶³ Two RCTs^{57,62} have shown reduced costs associated with the use of HMEs compared with HHs.

Provided there are no contraindications to their use (e.g. patients at risk of airways obstruction), we recommend that HMEs rather than HHs are used, as HMEs are more effective in reducing the incidence of VAP. Recommendation Grade A

When HMEs are used, the type chosen should be one that has adequate moisture output to minimize the risk of airway

obstruction. The benefit of use of HMEs versus HHs should be established for each patient and this decision should not be based solely on infection control considerations. **Recommendation Grade GPP**

National guidelines should be followed in respect of the use of humidifiers and HMEs for the management of patients with highly communicable infections, e.g. human coronavirus. **Recommendation Grade GPP**

2.2.4. Frequency of change of humidifiers

A systematic review⁴⁷ and three RCTs address this issue^{64–66} with two of the latter^{64,65} specifically evaluating the effect on VAP of a reduced frequency of change of the humidifier. One study that looked at efficacy and safety by studying three different types of HMEs reported that not all HMEs performed equally with only some brands able to be used for 48 h without change.⁶⁴ It has also been reported that changing HMEs after 3 days does not diminish the efficiency of the equipment or increase the incidence of VAP.⁶⁵ From these studies, there is no evidence that more frequent changing of HHs and HMEs than manufacturers recommend reduces the risk of HAP.

We recommend that where HHs and HMEs are used (except with high minute volume) these should not be changed routinely and manufacturer's guidance should be followed. Recommendation Grade A

The technical performance of HMEs for more than 48 h should be monitored, especially in patients with chronic obstructive pulmonary disease (COPD), and if there is evidence or suspicion of contamination, the humidifier should be changed. **Recommendation Grade GPP**

2.2.5. Nebulizers

Nebulizers are used both in the ICU and wards and departments to deliver bronchodilators and other drugs. Three diagnostic studies have reported that nebulizers can become contaminated and act as a source of respiratory tract infection.^{67–69}

We recommend that nebulizers should be single patient use and need to be disinfected and cleaned with sterile water between each use. Recommendation Grade D

Nebulizers used as part of the ventilator circuit should be single use only and national guidelines should be followed with regard to the use and cleaning of nebulizers. **Recommendation Grade GPP**

2.2.6. Filters

There are reports in the literature that provide evidence to support the use of filters to protect circuit systems from bacterial contamination,^{68,70,71} but there is no evidence which establishes that the use of filters specifically protects against HAP.

We recommend that appropriate filters are used to protect mechanical ventilator circuits from bacterial contamination. Recommendation Grade C

National guidelines should be followed with regard to the use of expiratory filters for patients suffering from highly communicable infections, e.g. human coronavirus, and who require mechanical ventilation. **Recommendation Grade GPP**

2.2.7. Suction equipment

Suctioning of patients on intensive care is essential to prevent pooling of respiratory secretions. A systematic review⁴⁷ and three other studies^{72–74} have examined the effect of daily changes of in-line suctioning equipment and found that when compared with less frequent changes, this had no effect on the incidence of VAP. Whereas there is, therefore, no evidence that changing closed suction equipment daily reduces the risk of VAP, the maximum duration that a closed suction catheter can be used against safety and infection control considerations is not known.

We recommend that daily change of suction equipment is not required. Recommendation Grade A

Suction equipment may be changed weekly unless it becomes contaminated or damaged, in which case it should be changed immediately. Recommendation Grade GPP

2.2.8. Resuscitation equipment

Four studies on use of bag-valve mask ventilation (manual ventilation/'Re-breathe') bags have reported that such resuscitation equipment can act as a source of HAP if it becomes bacterially contaminated.^{75–78}

We recommend that in order to minimize the risk of HAP multiuse, bag-valve mask ventilation (manual ventilation/'Re-breathe') bags should be decontaminated according to the manufacturer's guidelines between each patient use. Recommendation Grade C

All reusable resuscitation equipment should be appropriately decontaminated according to the manufacturer's recommendations after use and if possible single patient use equipment (e.g. Ambu bag) should be employed. **Recommendation grade GPP**

2.2.9. Anaesthetic machines and breathing equipment

A diagnostic study suggested that basic hygienic management of anaesthetic equipment was adequate to prevent cross-infection.⁷⁹ Studies are required to establish the best sterilization or disinfection and maintenance methods to reduce the risk of HAP from anaesthetic machines and breathing systems.

We recommend that to reduce the risk of HAP, basic hygienic measures should be adopted for anaesthetic equipment. Recommendation Grade D

Provided filters are in place to protect the equipment, anaesthetic equipment should be decontaminated according to the manufacturer's instructions. **Recommendation Grade GPP**

Changing HMEs and anaesthetic machine valve between patients and weekly circuit changes should be adequate to prevent infection from anaesthetic machines. Recommendation Grade GPP

If anaesthetic equipment is used on a known infected patient, tubing and filters should be changed before the next patient use. Recommendation Grade GPP

2.2.10. Pulmonary function testing equipment

There are reports of the use of spirometers being associated with HAP caused by *Acinetobacter* spp.^{80,81} One study reported that

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the mouthpieces of spirometry tubing can become contaminated with bacteria during use and recommended that to prevent the acquisition of microorganisms causing HAP they should not be shared between patients.⁸²

We recommend that spirometry mouthpieces should be single use only. Recommendation Grade C

All respiratory equipment, where contamination by respiratory secretions is possible, should be viewed as a potential infection risk for HAP and therefore precautions should be taken to reduce such risks. Recommendation grade GPP

2.3. Patient procedures

2.3.1. Closed versus open suctioning

Several studies have assessed the effect of closed versus open suctioning on VAP, but their results are not consistent. A systematic review⁴⁸ considered evidence from four RCTs^{83–86} and concluded that the type of suctioning system had no effect on the incidence of VAP. Two further RCTs confirmed these findings.^{87,88} However, one RCT reported a 3.5 times greater risk of VAP in patients receiving open versus closed suctioning.⁸⁴ Most studies, therefore, show that closed as opposed to open suctioning of respiratory tract secretions does not affect the risk of VAP and there is no evidence that closed suctioning increases the risk of VAP.

No recommendation can be made on the use of closed suctioning to reduce the risk of HAP to patients and we recommend that closed or open suctioning systems can be used without affecting the risk of VAP. Recommendation Grade B

From a safety perspective, closed suctioning of respiratory tract secretions is of value in reducing the aerosolization of respiratory tract secretions and protection of healthcare workers. The number of disconnections of suction equipment should be minimized to reduce the risk of exposure to staff to potentially infected secretions. Recommendation Grade GPP

2.3.2. Use of non-invasive positive pressure ventilation

NIV involves providing respiratory support to patients without the need for intubation. There is evidence that in selected patients NIV reduces the risk of HAP. A Cochrane systematic review⁸⁹ included five RCTs and found that in patients with COPD, NIV reduced the risk of HAP. Although the indications for this procedure are relatively narrow, the numbers of patients to whom they apply are large.

We recommend that to reduce the risk of HAP, NIV rather than mechanical ventilation should be used in appropriate patients. Recommendation Grade A

2.3.3. Method of ET intubation

One RCT⁹⁰ specifically addressed the issue of oral versus nasotracheal intubation with regards to the development of VAP, whereas this and four other RCTs^{91–94} also assessed the development of maxillary sinusitis. All these demonstrated an association between nasotracheal intubation and maxillary sinusitis. Another study showed that re-intubation is associated with an increased incidence of VAP.⁹⁵

We recommend that, where possible, oral ET intubation should be used in preference to nasotracheal intubation

and that re-intubation should be avoided if possible. Recommendation Grade C

2.3.4. Use of enteral feeding

Enteral feeding is used to prevent the development of a catabolic state in patients requiring long-term ventilation. A cohort study⁹⁶ of ventilated patients showed a relationship between enteral feeding and aspiration, but there is limited other evidence to support this. There is also an absence of evidence that the incidence of HAP in ventilated patients is reduced by taking measures to reduce aspiration associated with enteral feeding. In view of these findings, no recommendation can be made about the use of enteral feeding to prevent HAP.

We recommend that in ventilated patients, the rate and volume of enteral feeding should be adjusted to avoid gastric distension and so reduce the risk of aspiration. Recommendation Grade GPP

2.3.5. Different methods of enteral feeding

There are a number of methods of providing enteral feeding and these were assessed in a systematic review.⁹ Four RCTs that evaluated different methods of enteral feeding, which included intermittent feeding,⁹⁷ the use of metoclopramide and acidification of feeding, were reviewed. No difference in the incidence of VAP or mortality was found with any of these strategies. A meta-analysis⁹⁸ of seven RCTs looked specifically at post-pyloric feeding and reported that compared with gastric feeding this was associated with a significant reduction in VAP. It was suggested that further studies are warranted. A second meta-analysis⁹⁹ that included nine RCTs compared gastric versus post-pyloric feeding and found that there was no significant difference in the incidence of VAP in each group. Further research is required to study the effect of different modes of feeding on the incidence of HAP.

We recommend that as there is no clear evidence that intermittent feeding, small intestine feeding, the use of metoclopramide or acidification of feeding prevent VAP, the decision on the method of enteral feeding to be used for critically ill patients should be made locally by each unit and on an individual patient basis. Recommendation Grade A

When enteral feeding is used, the method of delivery should be optimized for each patient. Recommendation Grade GPP

2.3.6. Prevention of aspiration

The relationship between aspiration of gastric contents and pneumonia/pneumonitis is well known. Although there is an absence of evidence that prevention of aspiration associated with ET intubation reduces the incidence of HAP, a cohort study⁴ reported that witnessed aspiration was associated with an increased risk of VAP. A meta-analysis¹⁰⁰ found that establishing subglottic drainage was effective in preventing early-onset VAP in patients expected to remain ventilated for more than 72 h.

We recommend that to prevent VAP, measures should be taken to reduce the risk of aspiration and this should include subglottic drainage and positioning. Recommendation Grade B

Attention needs to be paid to the ET cuff pressure to avoid aspiration and prevent tracheal damage (>25 and <30 cm water).¹⁰¹ Recommendation Grade GPP

2.3.7. Use of sucralfate and stress ulcer prophylaxis

There is clear evidence that a reduction of gastric acid by various methods, including antacids and H₂ antagonists used for stress ulcer prophylaxis in ICU patients on ventilation, increases the risk of VAP. However, the literature is not consistent with regard to the use of sucralfate in this context. A systematic review⁹ that considered seven meta-analyses found evidence in four of these^{102–105} that sucralfate when compared with H₂ antagonists significantly reduced the incidence of VAP. The three other meta-analyses did not show a statistically significant reduction in VAP with the use of sucralfate, but did show a trend to this effect.^{106–108} A large RCT¹⁰⁹ found that in mechanically ventilated patients, sucralfate therapy was associated with a statistically significantly increased risk of clinically important gastrointestinal bleeding compared with H₂ antagonists. There is, therefore, evidence that the use of sucralfate is associated with a reduced risk of VAP when compared with the use of other agents that raise gastric alkalinity in ventilated patients, but sucralfate therapy has been associated with an increased risk of clinically important gastrointestinal bleeding when compared with ranitidine.

We recommend that whenever clinically appropriate, stress ulcer prophylaxis should be avoided in order to help preserve gastric function. Recommendation Grade A

We recommend that where stress ulcer prophylaxis is indicated, sucralfate is to be preferred in order to reduce the risk of VAP, but sucralfate should only be used in patients with low to moderate risk of gastrointestinal bleeding. Recommendation Grade A

2.3.8. Effect of breathing exercises

There is an absence of evidence that instructing patients to cough or take deep breaths reduces the incidence of HAP. Two cohort studies^{110,111} and an RCT¹¹² did not specifically look at HAP but considered pulmonary complications in general. Another study¹¹³ found that the most effective regimen of prophylaxis against pulmonary complications for low-risk patients after abdominal surgery was deep breathing.

We recommend that coughing and early mobilization during the post-operative recovery period should be encouraged in all patients in order to reduce the risk of pulmonary complications. Recommendation Grade GPP

2.3.9. Role of physiotherapists and respiratory therapists

We found no data on the role of physiotherapists and respiratory therapists in reducing the incidence of HAP in general. However, one study¹¹⁴ showed the benefit of chest physiotherapy in preventing VAP, whereas an RCT¹¹⁵ demonstrated that physiotherapy with incentive spirometry reduced respiratory complications in high-risk surgical patients. A systematic review¹¹⁶ assessed the role of respiratory therapists and reported five RCTs, which showed that respiratory therapists were effective in implementing respiratory care protocols to wean patients from mechanical ventilation and in appropriately allocating respiratory care in adult non-ICU patients but did not relate either of these features to HAP prevention. Therefore, there is evidence that respiratory therapists, by following weaning protocols, both reduce the duration of mechanical ventilation and ICU stay and improve

outcome. Also, physiotherapy with incentive spirometry in high-risk abdominal surgery patients can reduce respiratory complications, including pneumonia. Further research is required to establish the role of physiotherapy in the prevention and management of HAP.

We recommend that physiotherapists and respiratory therapists have a role in preventing respiratory complications in post-operative ventilated patients. Recommendation Grade A

Physiotherapists and respiratory therapists have a holistic role in the pre- and post-operative care of patients, especially in high-risk patients, where risk assessment indicates this may be of value. Recommendation Grade GPP

2.3.10. Use of incentive spirometry

There is some evidence that the use of incentive spirometry in post-operative, high-risk surgical patients may be beneficial, although this is poor, with only one RCT.¹¹⁵ There is an absence of evidence that incentive spirometry has any impact on reducing the risk of HAP in low-risk surgical patients after abdominal surgery. Further research is required to assess the effects of incentive spirometry in patients requiring surgery.

We recommend that incentive spirometry has no role to play in prevention of HAP in the low-risk (ASA grade 1 or 2) surgical patient, including patients who had no pre-existing pulmonary complications, and that it should be used in high-risk patients to prevent respiratory complications. Recommendation Grade D

2.3.11. Positional strategies

Several studies have looked at the use of semi-recumbent, prone and supine positioning in relation to the risk of HAP. An RCT¹¹⁷ found that the use of semi-recumbent positioning may prevent VAP and also reported that supine body positioning and enteral feeding were independent risk factors for the development of nosocomial pneumonia (NP). However, an earlier study¹¹⁸ with a smaller number of patients concluded that the semi-recumbent positioning did not prevent VAP. Another RCT¹¹⁹ looked at the effect of prone positioning on patients with acute respiratory failure and found that there was no general benefit from using prone positioning and that there were concerns about safety. However, a cohort study¹²⁰ showed that patients nursed in supine head positioning during the first 24 h of ventilation had an increased risk of VAP. A further study¹²¹ reported a significant increase in VAP in patients transported out of ICU for interventions, which was most likely related to positioning.

We recommend that a positional strategy should be adopted to prevent VAP. If a patient does not require to be supine, and provided there are no contraindications, consideration should be given to using the semi-recumbent position (30–45°) as a strategy to prevent VAP. Recommendation Grade B

Consideration should be given to adopting a positional strategy to prevent HAP in non-ventilated patients. Recommendation Grade GPP

Patients on ventilation being transported out of ICU should if possible be maintained in the semi-recumbent position. Recommendation Grade GPP

In order to prevent aspiration, patients should be kept in a semi-recumbent position during enteral feeding. GPP

2.3.12. *Use of kinetic beds (oscillatory therapy)*

There is a limited amount of evidence on the use of kinetic beds to prevent HAP. A meta-analysis,¹²² which included six studies, and a systematic review⁴⁸ covering eight RCTs have reviewed the use of kinetic (oscillating) beds. Their conclusion was that although these may have an impact on reducing complications associated with intensive care, it is inconclusive whether they affect the development of HAP. At present no recommendation for use of kinetic therapy to prevent HAP can be made from the evidence and further research is required to assess the value of kinetic therapy in the prevention of HAP in different patient populations and especially in ICUs.

2.3.13. *Use of red cell transfusions*

The use of transfusions has been particularly studied in post-operative patients and those receiving intensive care. One study¹²³ demonstrated that transfusion of >4 U or red cell concentrate was associated with an increased risk of HAP in cardiac surgery patients, whereas another cohort study showed that the use of stored red blood cells increased the risk of HAP.¹²⁴ In contradistinction, a study¹²⁵ reported that a restrictive transfusion policy in ICU patients is at least as effective as a liberal policy with regard to the effect on mortality and multiorgan failure. Finally, a cohort study reported that leucocyte-depleted blood was better than buffy-coat reduced blood in preventing pneumonia in patients undergoing colorectal surgery.¹²⁶ There is, therefore, some evidence that the use of red cell transfusions increases the risk of HAP and the evidence available is particularly applicable in cardiac and colorectal surgery. Further research needs to be carried out to establish the effect of red cell transfusions on the development of HAP in other patient groups.

We recommend that to prevent HAP, red cell transfusions should be avoided if possible and if used should be with fresh red cells. Recommendation Grade C

2.4. *Environmental issues*

2.4.1. *Methods to reduce transmission of Aspergillus during building work*

There are a number of studies that demonstrate an association between building works, environmental contamination with *Aspergillus* and pulmonary aspergillosis.^{127–129} There is good evidence that methods to reduce dust levels result in lower levels of fungal spores in the environment and reduce the incidence of pulmonary aspergillosis during building work. However, there are no studies that systematically look at the risk in relation to the type of building work (construction versus demolition) and relative contributions of various strategies to reduce risk, i.e. (i) dust reduction, (ii) air handling, (iii) environmental and air monitoring, and (iv) antifungal prophylaxis.

There is a financial impact if measures other than simple dust reduction are used and introducing widespread environmental control is expensive, e.g. HEPA filtration. Moreover, there is an absence of evidence that routinely monitoring spore counts during building work is useful, although it is recommended by

some authors, especially for high-risk areas.^{130–132} Studies have shown that although a protective environment with HEPA filtration reduces the incidence of invasive aspergillosis (IA) in haemopoietic stem cell transplant (HSCT) patients, this may not by itself prevent IA during building work.^{131,132}

We recommend that during building works, consideration is given to addressing the risk of pulmonary aspergillosis. This must include:

- Identifying high-risk patients, i.e. those with acute leukaemia, HSCT patients, patients receiving chemotherapy resulting in severe, prolonged neutropenia and other immunosuppressed patients including those on long-term corticosteroids or other immunosuppressive therapy.
- Methods to reduce all patient's exposure to *Aspergillus*, e.g. use of floor to ceiling barriers, sealing of windows.
- The use of HEPA filtration in high-risk units, e.g. HSCT units and critical care.
- Dust reduction in clinical areas including cleaning (damp dusting, use of HEPA-filtered vacuum cleaners).

Recommendation Grade B

The routine monitoring of air for fungal spores during building work outside high-risk areas is not recommended. Recommendation Grade D

During building work, environmental monitoring for fungal spores in critical areas housing at-risk patients is useful in monitoring the effectiveness of control measures. Recommendation Grade GPP

In an outbreak situation, environmental or air monitoring may be useful in identifying the source of infection. Recommendation Grade GPP

Ventilation systems, especially those which are not HEPA filtered, may become contaminated during building work. During building work, all filters should be regularly inspected and replaced as necessary. Recommendation Grade GPP

2.4.2. *Use of prophylactic antifungal agents during building work*

As there have been several outbreaks of *Aspergillus* infection associated with building work, this raises issues regarding additional patient-focused methods that can be used to prevent infection, including the use of antifungal agents. There is no good evidence for the widespread use of antifungal treatment as prophylaxis during construction work. A small cohort study¹³³ reported that antifungal prophylaxis in immunocompromised patients during construction work reduced IA. There is good evidence for the protective effect against IA of antifungal prophylaxis for neutropenic patients in general^{134,135} and specifically to support the use of itraconazole in this situation.^{134,136,137} There is no clear evidence-based indication against the use of any antifungal prophylaxis.¹³⁸

We recommend that where there is a high institutional rate of IA or building work is underway, a risk assessment should be undertaken. Those patients who are immunosuppressed, especially those who are neutropenic (neutrophil count <0.5 × 10⁹/L for more than 2 weeks or <0.1 × 10⁹/L for 1 week), who are visiting hospital regularly or staying as an inpatient but not in a HEPA-filtered environment

should be considered for antifungal prophylaxis.¹³⁹
Recommendation Grade D

The use of antifungals to prevent IA in the immunosuppressed during building work should be based on a robust risk assessment for the individual patient. **Recommendation Grade GPP**

The cost of using antifungal prophylaxis should therefore be considered in all building projects (cost of drug and monitoring). In large hospital projects, e.g. involving demolition and reconstruction, the additional cost may need to cover several months. **Recommendation Grade GPP**

2.4.3. *Legionella* control

There is a good evidence base showing a relationship between *Legionella* contamination of hospital water with hospital-acquired (HA) *Legionella* pneumonia and also good evidence that controlling the risk of *Legionella* in hospital water supplies reduces the risk of HA *Legionella* pneumonia. There is a large body of evidence regarding methods to control *Legionella* in hospital water supplies consisting of cohort and case-control studies.^{140–149} The Health and Safety Executive (HSE) has also issued comprehensive guidance on the control of *Legionella* in hospitals,¹⁵⁰ which has recently been reevaluated.¹⁵¹

The methods available to control *Legionella* in water systems include: (i) heat; (ii) biocides, e.g. chlorine, chlorine dioxide; (iii) ionization, e.g. copper-silver; and (iv) ultraviolet light and ozone.

There are few studies comparing the different methods. Results across the methods are consistent in demonstrating that each process has an effect in reducing *Legionella* load in hospital waters although the effect may be only temporary. However, it is not possible to make full comparisons between the different methods. Hospitals should already be adhering to DH advice for control of *Legionella* in hospitals so there should be no additional financial consequences. Research is required to confirm the relationship between environmental *Legionella* and HA Legionnaire's disease, including establishing the relative importance of different serogroups of *Legionella pneumophila* and other *Legionella* spp. Research is required into the different methods of controlling *Legionella* appropriate for use in different healthcare settings.

Although no recommendation can be made about the most appropriate method, we recommend that in line with the current guidance, appropriate *Legionella* control of hospital water is required. **Recommendation Grade B**

UK HSE guidance on Legionnaires' disease—control of *Legionella* bacteria in water systems^{150,151} and all other national guidance should be followed. **Recommendation Grade GPP**

For secondary prevention (i.e. preventing further cases after a case of hospital-acquired infection), additional measures may be required, e.g. use of biocides, heat flush etc. **Recommendation Grade GPP**

Routine culturing of hospital water for *Legionella*, while not recommended, is appropriate in high-risk area, e.g. for haemopoietic stem cell and solid organ transplant wards. Infection control teams should work closely with hospital engineers, management and physicians to ensure awareness of HA Legionnaires' disease.¹⁵² **Recommendation Grade GPP**

2.4.4. Cleanliness of the environment

Cleanliness of the environment has been highlighted by the DH 'Saving Lives' initiative as essential to prevent HCAI.⁵ There are a small number of cohort studies that demonstrate environmental risk related to poor cleaning, e.g. for infection with methicillin-resistant *Staphylococcus aureus* (MRSA) and *Clostridium difficile*, but these do not relate directly to HAP or specifically to ICUs. There are a small number of studies that describe the environment acting as a reservoir for other organisms causing infection in patients, though these also do not relate directly to HAP or ICUs. These studies demonstrate that taking action to remove the reservoir is effective in preventing infections. The *epic* project review revealed little research evidence of an acceptable quality upon which to base guidance relating to hospital environmental hygiene.³⁹ However, it noted that there is a large body of clinical evidence, derived from case reports and outbreak investigations, which show links between poor environmental hygiene and the transmission of microorganisms causing HCAI.^{153,154}

Given that the routes of transmission for organisms causing HAP are different from those described in the available reports, where the issues relate mainly to direct contact and contamination spread, the applicability of the available evidence, which does not directly relate to HAP, is not strong. It is not possible to generalize from the available evidence as this is of a low volume and not directly related to HAP, ICUs or in all instances, cleaning. The small volume of research that is available is consistent in demonstrating that the environment can act as a reservoir for infection and that taking action to remove the reservoir is effective in preventing infection. The consistency of the evidence makes extrapolation to these issues reasonable. There are now published cleanliness standards for health-providing facilities and these form part of performance assessment reviews.^{155,156}

We recommend that in order to reduce the risks of HCAI (including HAP), good approved standards of hospital cleanliness should be maintained. Recommendation Grade D

The hospital environment must be visibly clean, free from dust and soilage and acceptable to patients, their visitors and staff. Recommendation Grade GPP

All staff involved in hospital hygiene activities should undergo education and training related to the prevention of HCAI: such training to include the link between these infections and the cleanliness of the environment. Recommendation Grade GPP

3. Diagnosis

3.1. General issues in the diagnosis of HAP

3.1.1. Definitions of HAP

HAP (or NP) is usually defined as pneumonia developing ≥ 48 h after admission to hospital that was not incubating at the time of admission.^{7,157,158} VAP is usually defined as pneumonia developing ≥ 48 h after implementing ET intubation and/or mechanical ventilation that was not present before intubation.^{3,7,157–160}

HAP can be divided into early- and late-onset. Early-onset disease occurs within 4–5 days of admission and tends to be caused by antibiotic-susceptible community-type pathogens,

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whereas late infections tend to be caused by antibiotic-resistant hospital opportunists. However, some studies have found an increasing frequency of early-onset HAP caused by pathogens more commonly associated with nosocomial disease. This has contributed to the concept of healthcare-associated pneumonia (HCAP), involving pathogens associated with recent prior hospitalization and/or antimicrobial therapy. HCAP has been defined as pneumonia occurring in any patient who had been admitted to an acute care hospital for 2 or more days within 90 days of the infection; or had been a resident in a nursing home or long-term care facility; or had attended a hospital or haemodialysis clinic; or had received recent intravenous antibiotic therapy, chemotherapy, or wound care within the past 30 days of the current infection.⁷ Rarely, HAP/VAP is due to fungal infection and this is usually, although not exclusively, seen in severely immunocompromised patients.

VAP also can be divided into early- and late-onset. Early-onset VAP occurs during the first 4 days of mechanical ventilation when the pneumonia is often caused by typical community organisms. Late-onset VAP develops ≥ 5 days after the initiation of mechanical ventilation and is commonly caused by typical opportunistic and antibiotic-resistant hospital pathogens such as *P. aeruginosa* or MRSA.^{3,158,159}

3.1.2. Issues in assessing the literature on diagnosis of HAP

There are two fundamental problems with assessing the diagnostic literature relating to HAP. The first is that most publications deal with VAP, whereas most HAP occurs in non-ventilated and non-intubated patients. It may not be valid to extrapolate diagnostic criteria for VAP to HAP; for example, the diagnosis of VAP often involves invasive microbiological sampling, which may not be possible or appropriate in non-intubated patients. The second problem is that there are no universally accepted 'gold' or reference standard diagnostic criteria for HAP or VAP. Because of this, it is difficult to compare different diagnostic methods. Most studies begin by dividing patient groups into those with pneumonia and those without, but the criteria used for this division vary, and all have their problems. Thus, most studies have groups of patients that *probably* have pneumonia or *probably* do not, and in each there is an unknown proportion that will have been wrongly classified. For example, some patients, not thought to have HAP clinically, have been diagnosed at autopsy,¹⁶¹ and vice versa. We have not excluded such studies from this analysis, but have interpreted the results with caution. Recently, more useful studies have appeared that avoid these problems by analysing the outcomes of management based on different diagnostic techniques in a single group of patients suspected of having HAP.

3.1.3. An assessment of lung histology and culture as a reference standard for the diagnosis of HAP

As lung biopsies are impractical and associated with risk, they are rarely used for the diagnosis of HAP and are not recommended for this purpose. Nevertheless, histology and cultures of homogenized lung tissue have frequently been used to validate other diagnostic tests such as the quantitative microbiology of respiratory specimens.

An experimental baboon model of VAP has been used to assess the severity of bronchopneumonia by lung histology and

to compare this with quantitative microbiology of lung tissue and bronchoalveolar lavage (BAL) specimens.¹⁶² Moderate/severe pneumonia as judged by histology was associated with high bacterial concentrations in homogenized lung biopsies, and bacterial concentrations in BALs were linearly related to tissue values. This led to the concept that quantitative bacteriology of a BAL or other deep respiratory specimen could be used for the accurate diagnosis of HAP/VAP. Many subsequent studies of pneumonia in human patients have used lung histology (or quantitative microbiology of respiratory secretions) as the reference standard for assessment of other diagnostic methods.

However, several studies of lung biopsy and culture have shown inconsistent results. In a prospective case study, post mortem lung biopsies were performed < 1 h after death on 39 patients who had been mechanically ventilated for ~ 14 days.¹⁶³ Histological pneumonia was diagnosed by four independent pathologists in 7, 9, 12 and 15 cases (18% to 38%), respectively. One of the pathologists reviewed the slides blindly 6 months later and re-classified two patients (one diagnosed with and one without pneumonia). A single pathologist then reviewed the slides by the Johanson *et al.*¹⁶² criteria and diagnosed pneumonia in 14 patients (36%).¹⁶³ A later prospective case study of quantitative microbiology of open lung biopsies of ventilated patients found that histological lesions of pneumonia and tissue concentrations of bacteria were unevenly distributed through the lung parenchyma.¹⁶⁴ Quantitative tissue bacterial concentrations tended to correlate with the presence and severity of histological lesions, but could not differentiate the histological presence or absence of pneumonia. Similar results have been obtained by others.^{165–167}

We recommend that lung histology should not be relied upon as a gold/reference standard for the diagnosis of HAP. Recommendation Grade D

When biopsy is used as the reference standard for other diagnostic methods in HAP, the histological criteria should be standardized. Recommendation Grade GPP

The histological diagnosis of HAP or quantification of bacterial lung tissue concentrations should be based on several specimens from different areas of the lung. Recommendation Grade GPP

Studies using histology or parenchymal cultures as the reference standard for assessment of other diagnostic criteria in HAP should be interpreted with caution. Recommendation Grade GPP

3.2. The clinical diagnosis of HAP

3.2.1. Clinical diagnostic criteria

The clinical diagnosis of pneumonia, HAP and VAP is difficult and there are no universally accepted clinical criteria. A systematic review covering the clinical diagnosis of VAP considered publications up to 1998,¹⁶¹ whereas other evidence comprises cohort studies^{168,169} or consensus opinion.⁸

Clinical diagnostic criteria described in consensus opinion statements^{3,8,158,170} are the same for VAP, HAP and community-acquired pneumonia (CAP). However, there is overlap of clinical signs and symptoms between pneumonia and other forms of sepsis, and the diagnosis of HAP often cannot be made on clinical criteria alone.

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With these reservations, the diagnostic sensitivity of clinical suspicion can be improved by taking account of the presence of fever (core temperature $>38.3^{\circ}\text{C}$), blood leucocytosis ($>10\,000$ leucocytes/ mm^3) or leucopenia ($<4000/\text{mm}^3$), purulent tracheal secretions and the presence of a new and/or persistent infiltrate on chest radiograph (CXR), which is otherwise unexplained.¹⁶¹ However, if all these clinical criteria were required for diagnosis, the specificity would be poor.¹⁶¹ A European consensus group¹⁷⁰ believed that a diagnosis of pneumonia could be based on pulmonary infiltrates plus two of the other criteria.

In some patients, increasing severity of pneumonia may be associated with increasing evidence of circulatory collapse (shock, tachycardia, hypotension and elevated blood urea concentrations).^{171,172} However, these signs of sepsis are not specific for pneumonia and are not required for diagnosis of HAP or VAP. In a comparative study, immediate post mortem histology in 39 patients who had been mechanically ventilated for ~ 14 days was assessed against five clinical diagnostic criteria (fever, leucocytosis, positive sputum culture, worsening CXR changes and worsening gas exchange).¹⁷³ None of the individual clinical criteria or any combination of them correlated with the presence or absence of histological pneumonia. Thus, there is only a moderate amount of evidence comparing clinical diagnostic criteria with reference criteria, including histology, and these data demonstrate that there can be considerable variation in the clinical presentation of HAP and that distinction from other forms of sepsis is difficult.

3.2.2. *The clinical pulmonary infection score*

The clinical pulmonary infection score (CPIS) is an evolving clinical scoring system approach to the diagnosis of HAP. It is now based on six criteria [the original four—fever, leucocytosis, positive sputum culture and worsening CXR changes—plus oxygenation ($\text{PaO}_2/\text{FiO}_2$) and semi-quantitative cultures of tracheal aspirates with or without Gram's stain]. These developments have been claimed to further increase diagnostic sensitivity.^{174,175} A prospective case series¹⁷⁶ studied 25 deceased patients who had been mechanically ventilated before death. The presence of both histological pneumonia and positive lung cultures immediately post mortem was used as a reference test for VAP. In these patients, the CPIS was not superior to conventional clinical criteria for the diagnosis of VAP before death. A prospective cohort study¹⁶⁹ investigated the utility of a modified CPIS in the diagnosis of HAP. Conventional clinical diagnosis was found to be inaccurate (sensitivity 50%, specificity 58%) and the CPIS was only slightly more accurate (sensitivity 60%, specificity 59%). Adding a Gram's stain result from a BAL specimen slightly increased the accuracy of both conventional (sensitivity 85%, specificity 49%) and CPIS (sensitivity 78%, specificity 56%) diagnosis. However, although the CPIS has not been shown to improve diagnostic accuracy compared with conventional clinical assessment, it has been used successfully to monitor and modify therapy. A prospective, multicentre cohort study¹⁷⁷ of ventilated patients with suspected VAP used serial measurements of CPIS to monitor the clinical course of VAP and successfully identified patients with a good prognosis by day 3. A further study¹⁷⁸ investigated patients with pulmonary infiltrates with suspected VAP but with a CPIS score of ≤ 6 (low likelihood of pneumonia). Patients were randomized to receive standard therapy or ciprofloxacin monotherapy with

discontinuation at day 3 if the CPIS remained ≤ 6 . Compared with patients on standard therapy, those on ciprofloxacin monotherapy had significantly lower antimicrobial costs, antimicrobial resistance and superinfections but no difference in length of stay or mortality. The authors concluded that the CPIS could be used to identify patients who would benefit from a short course of antibiotics.

We recommend that although the clinical diagnosis of HAP is difficult, the following criteria will identify patients in whom pneumonia should be considered in the differential diagnosis:

1. Purulent tracheal secretions, and new and/or persistent infiltrate on CXR, which is otherwise unexplained
2. Increased oxygen requirement
3. Core temperature $>38.3^{\circ}\text{C}$
4. Blood leucocytosis ($>10\,000/\text{mm}^3$) or leucopenia ($<4000/\text{mm}^3$) Recommendation Grade C

We recommend that the CPIS may be useful for selecting patients for short-course therapy and for monitoring response to treatment. Recommendation Grade C

3.3. *The radiological diagnosis of HAP*

There is little available evidence to assess the value of imaging investigations in the diagnosis of HAP and VAP. There is only one systematic review¹⁷⁹ that, with other reviews of diagnostic studies, focuses on VAP and not the broader topic of HAP.^{170,174,180–182}

Publications on diagnostic imaging in VAP/HAP have been mainly limited to the use of CXR and there is little information on other techniques such as computed axial tomography (CT), magnetic resonance (MR) and positron emission tomography (PET). These newer techniques are not useful for initial investigations. CT can be useful as an additional diagnostic tool to exclude other pathology in a patient with a complex CXR, but the role of MR and PET in the diagnosis of HAP/VAP has not been assessed. The diagnostic value of CXR is usually greater in HAP than VAP, because of the problems of performing mobile radiographic investigations on ventilated patients who cannot be moved and because of other cardiothoracic co-morbidities often present in such patients. Ventilated patients may have abnormal CXR secondary to other pathology that must be distinguished from infection, e.g. acute lung injury, left ventricular failure, aspiration or alveolar haemorrhage. Radiological investigations of patients with VAP do not often influence outcome and are more useful in patients with non-ventilated HAP where they may provide information on differential diagnosis, complications or the exclusion of other pathology. Therefore, although the presence of an alveolar infiltrate on the CXR raises the possibility of HAP as well as other differential diagnoses, there are no key imaging investigations that can establish the diagnosis of HAP, though a normal CXR excludes HAP.

We recommend that when a diagnosis of HAP is being considered, a good quality CXR should be obtained and compared with previous CXRs if available. Recommendation Grade D

CT scanning may assist in the differential diagnosis of HAP and may guide management in patients who are not responding to treatment and who have a complex CXR. Recommendation Grade GPP

3.4. The microbiological diagnosis of HAP

3.4.1. The microorganisms of HAP

The literature on the microbiology of HAP/VAP is extensive, consisting mainly of observational studies based on surveillance epidemiology. A wide range of bacteria are associated with HAP and VAP (Tables 2 and 3).^{3,183–186} The most common organisms isolated from respiratory specimens of patients known or suspected to have HAP are *P. aeruginosa*, *S. aureus* and Enterobacteriaceae (especially *Klebsiella*, *E. coli* and *Enterobacter* spp.). Polymicrobial cultures are common in VAP, occurring in up to 60% of the case studies³ with anaerobes and fungi being uncommon. Many microbial surveillance studies have used quantitative microbiology of specimens collected by invasive techniques, but there is no agreement on criteria to distinguish colonization from infection. Many studies simply report isolates without an assessment of their significance and these culture results should be interpreted with caution.

The longer a patient is in hospital, the wider the spectrum of likely pathogens and the more likely they are to be multiple drug resistant. Early-onset HAP or VAP is often caused by typical antimicrobial-susceptible community organisms such as *Streptococcus pneumoniae* or *Haemophilus influenzae*. Late-onset HAP or VAP is commonly caused by *P. aeruginosa* or other antimicrobial-resistant opportunistic Gram-negative bacteria or by MRSA.^{3,158,159} However, some studies have found an increasing frequency of early-onset HAP caused by nosocomial pathogens, probably resulting from recent prior hospitalization and/or antimicrobial therapy and referred to as HCAP (see Section 2.1.).^{7,186,187} Resistance rates in nosocomial pathogens of all kinds are increasing, particularly in ICUs.^{188,189} This trend

Table 2. Frequency of organisms (%) isolated from patients with suspected HAP in the US; National Nosocomial Infections Surveillance System (NNISS—1985–97),^{183,184} the European EPIC study (1992)¹⁸⁵ and the Eole French study (2002)¹⁸⁶

Pathogen	Study				
	NNIS (USA)			EPIC	Eole
	1985–88	1989	1992–97	(Europe) 1992	(France) 1997–98
<i>P. aeruginosa</i> /spp.	17.2	16	21	29.8	17
<i>Escherichia coli</i>	6.4	4	4	6.8	13
<i>Klebsiella</i> spp.	7.4	7	8	8	4
<i>Enterobacter</i> spp.	10.4	11	9	8	4
<i>Serratia</i> spp.	4.5	—	4	—	4
Other enterobacteria	—	—	4	—	—
<i>H. influenzae</i>	6.4	5	—	10.2	19
<i>Acinetobacter</i> spp.	—	4	6	10	2
<i>S. aureus</i>	14.6	20	20	31.7	27
Other staphylococci	—	—	1	10.6	7
<i>S. pneumoniae</i>	—	—	—	—	10
Other streptococci	—	—	2	—	10
Enterococci	—	—	—	—	—
<i>Candida albicans</i>	—	5	5	14	1

Table 3. Distribution of organisms isolated from cases of ventilator-associated pneumonia by bronchoscopic techniques in 24 studies (1989–2000) including 1689 episodes and 2490 pathogens³

Pathogen	Frequency (%)
<i>P. aeruginosa</i>	24.4
<i>Acinetobacter</i> spp.	7.9
<i>Stenotrophomonas maltophilia</i>	1.7
Enterobacteriaceae ^a	14.1
<i>Haemophilus</i> spp.	9.8
<i>S. aureus</i> ^b	20.4
<i>Streptococcus</i> spp.	8.0
<i>S. pneumoniae</i>	4.1
Coagulase-negative staphylococci	1.4
<i>Neisseria</i> spp.	2.6
Anaerobes	0.9
Fungi	0.9
Others (<1% each) ^c	3.8

^aDistribution when specified: *Klebsiella* spp., 15.6%; *Escherichia coli*, 24.1%; *Proteus* spp., 22.3%; *Enterobacter* spp., 18.8%; *Serratia* spp., 12.1%; *Citrobacter* spp., 5.0%; *Hafnia alvei*, 2.1%.

^bDistribution when specified: methicillin-resistant *S. aureus*, 55.7%; methicillin-susceptible *S. aureus*, 44.3%.

^cIncluding *Corynebacterium* spp., *Moraxella* spp. and *Enterococcus* spp.

is reflected in increasing resistance in respiratory isolates from HAP, especially in late-onset VAP.^{187,190,191} However, the relative frequency of the organisms involved varies between locations and dates of studies (Table 2).^{3,181–186,192}

Although no direct evidence-based recommendation can be made on microbiological surveillance data, we recommend that the assessment of the causal pathogens of HAP and their therapy should be guided by published national and international literature, local surveillance data and results of microbiological investigations in the individual patient. Recommendation Grade GPP

Not all organisms isolated from respiratory specimens in individual patients should be regarded as pathogens that necessarily require therapy; they should be interpreted and treated in the light of the full clinical picture, if necessary after consultation between microbiologists and clinicians. Recommendation Grade GPP

When probable (universally accepted) pathogens such as pneumococci are isolated from respiratory specimens in patients with suspected HAP, they should be treated. Recommendation Grade GPP

3.4.2. The contribution of blood cultures in the diagnosis of HAP

Blood culture isolates that are not contaminants are generally regarded as significant pathogens that require treatment. However, a prospective observational study¹⁹³ of 162 ICU patients with evidence of VAP found that there was a poor correlation between organisms isolated from blood cultures and those from BALs. In this study, bacteraemia was not associated with increased complications, length of stay, severity of illness or

mortality. The authors concluded that organisms isolated from the blood are not necessarily those causing VAP.¹⁹³

We recommend that when considering a diagnosis of HAP, the significance of blood isolates should be reviewed in the light of the patient's clinical condition during consultations between clinicians and microbiologists. Recommendation grade GPP

3.4.3. An assessment of microbiological sampling methods

The microbiological investigation of HAP includes microscopy and qualitative and quantitative culture of respiratory secretions. Sputum is a poor diagnostic specimen because it may not come from the infected area and it can be contaminated by upper respiratory flora during collection. To obtain specimens that more accurately reflect the bacterial burden deep within the lung, methods have been developed to collect lower respiratory samples and protect them from oro-pharyngeal contamination. These include bronchoscopy-directed methods and non-bronchoscopic 'blind' techniques. The most commonly analysed directed methods are bronchoscopy-directed BAL and bronchoscopy-directed protected specimen brush (PSB) sampling. Common non-directed methods are 'blind' BAL and ET aspiration. Many studies have compared qualitative and quantitative microbiological results on lower respiratory specimens obtained by different sampling methods. Most of these studies are of VAP.

3.4.3.1. Bronchoscopy-directed PSB and BAL. There are several high-quality reviews of the diagnostic value of quantitative cultures of respiratory secretions collected with bronchoscopy-directed PSB or BAL. A systematic review¹⁹⁴ of studies of directed PSB up to 1995, a similar review¹⁹⁵ of directed BAL analysing papers up to 1998 and a meta-analysis¹⁹⁶ assessing PSB and BAL studies up to 1994, all concluded that there was no significant difference between the diagnostic accuracy of quantitative microbiology specimens collected by bronchoscopy-directed PSB or BAL.

3.4.3.2. Blind PSB and BAL. A systematic review¹⁹⁷ of studies up to 1998 of blind bronchial sampling, blind mini-BAL and blind sampling with PSB for the diagnosis of VAP found that the diagnostic accuracy of blind sampling was similar to that of bronchoscopy-directed methods and side effects were also similar. Two more recent cohort studies have shown no significant difference between the use of bronchoscopic PSB, blind PSB and bronchoscopic BAL,¹⁹⁸ and no difference between blind and directed protected telescoping catheter and bronchoscopic BAL.¹⁹⁹ From this evidence, it can be concluded that there is no difference between the results obtained with PSB and BAL, and there is no advantage in using bronchoscopically directed methods compared with blind sampling.

3.4.3.3. Endotracheal aspirates (EAs). EAs are attractive specimens for microbiological sampling, since they are simple and safe to obtain by unskilled staff. A systematic review²⁰⁰ of reports published from 1985 to 1995 on the accuracy of EA cultures for the diagnosis of VAP concluded that the sensitivity and specificity of quantitative EA cultures varied widely (sensitivity 38% to 100%, and specificity 14% to 100%). Qualitative EA cultures had a high sensitivity, moderate positive predictive value and high negative predictive value. The authors concluded that

EA cultures were unreliable for the diagnosis of VAP. The use of EA samples has been analysed in three more-recent papers. In a study¹⁹⁹ of ventilated trauma patients with strong clinical and radiological evidence of VAP, an assessment was made of sampling respiratory secretions by EA, directed PSB, blind protected brushing via ET tube and bronchoscopy-directed BAL. The value of quantifying the percentage of infected cells in specimens by Gram's stain was also analysed. There was moderate agreement by kappa (κ) analysis between quantitative cultures of EA and BAL, and the sensitivity and specificity of quantification of infected cells in EA samples, using quantitative culture of BAL as the standard, were 96.7% and 48.9%, respectively. Another cohort study²⁰¹ identified patients with VAP based on clinical evidence and culture results of BAL and evaluated the significance of quantitative cultures with a diagnostic threshold of $>10^5$ cfu/mL for EA and $>10^4$ cfu/mL for BAL. From this study the reported sensitivities, specificities, positive predictive values, negative predictive values and correct classification (into pneumonia or not pneumonia) were EA: 82%, 67%, 82%, 67% and 77%; and BAL: 94%, 100%, 100%, 90% and 96%, respectively. Thus, EA performed less well than BAL, with similar sensitivities, lower specificities and fewer correct classifications.

Another study²⁰² evaluated the diagnostic value of Gram's stain identification of intracellular organisms in EA samples from ventilated patients. This used two cut-off points of 5% and 7% infected cells, with the usual trade-offs between sensitivity and specificity. In comparison with quantitative cultures of the same EA samples, the presence of intracellular organisms in $>5\%$ of cells had a sensitivity of 39% to 85%, specificity 82% to 97%, positive predictive value 70% to 96% and negative predictive value 50% to 91%. When outcome was considered, 10/35 patients (28.5%) were eventually treated for VAP by the attending physician; all had EA intracellular organism counts $\geq 5\%$ and quantitative cultures of $\geq 10^4$ cfu/mL from at least one specimen. However, 11/25 (44%) patients not treated for pneumonia had intracellular counts $\geq 5\%$. These studies support the conclusions that EA specimens have a high sensitivity for identifying bacteria in respiratory specimens, but they have a low specificity and have not been demonstrated to improve patient management.²⁰⁰ Thus, the evidence does not support the use of EA specimens for the diagnosis of VAP/HAP, either by culture or microscopy, quantitatively or qualitatively.

We recommend that EA cultures are not used for the diagnosis of VAP. Recommendation Grade A

We recommend that there is no evidence that any one invasive sampling method is better than any other. Recommendation Grade A

We recommend that the least expensive, least invasive and most rapid sampling technique requiring minimal expertise should be used for establishing the microbiological diagnosis of HAP, e.g. non-bronchoscopy-directed (blind) BAL. Recommendation Grade GPP

3.4.3.4. The role of quantitative microbiology in the diagnosis of HAP/VAP. Although a large amount of data assessing the diagnostic accuracy of quantitative microbiology has been published, little of it is of a high quality. A central problem is that there is no good reference standard for the diagnosis of HAP. Microbiological results have usually been compared with one or a combination of clinical, other microbiological (e.g. tissue) and histological diagnoses, but as described above, none of these

reference standards is reliable. A wide variety of invasive sampling techniques and quantitative microbiological criteria (cut-off points) have been used. EAs are not reliable for microbiological analysis, whereas, as described above, other sampling methods give similar results to each other.

A systematic review series on the use of quantitative microbiology for the diagnosis of HAP/VAP reviewed PSB¹⁹⁴ and BAL,¹⁹⁵ whereas a meta-analysis reviewed the use of PSB specimens.¹⁹⁶ There are also three consensus reviews^{53,169,170} and four good quality general reviews on this topic.^{3,7,203,204} In one systematic review,¹⁹⁵ the sensitivity of quantitative BAL culture ranged from 42% to 93%, with a mean of 73%; the specificity ranged from 45% to 100%, with a mean of 82%. Thus, false-negative results occur in about 25% of cases and false positives in about 20%. The other reviews have similar findings. However, an evidence-based guideline⁷ has concluded that negative lower respiratory tract cultures in patients with no recent change in antibiotic therapy is an indication for stopping antibiotics (study-defined evidence level 'moderate'). There is good repeatability when BAL specimens are analysed qualitatively but not quantitatively.²⁰⁵ Although lavage specimens are usually taken from one lung, there is evidence that bilateral lavage may be more accurate.²⁰⁶ Thus, quantitative cultures of respiratory specimens do not improve the diagnosis of HAP/VAP. These methods have a wide range of accuracy and a high likelihood of false-negative and false-positive results. They misdiagnose HAP/VAP in 20% or more of cases.

Although they may provide an indication to the causal pathogen, we recommend that quantitative cultures of respiratory specimens such as PSB and BAL should not be relied on for the diagnosis of HAP/VAP. Recommendation Grade A

3.4.3.5. Quantification of intracellular organisms in the diagnosis of HAP. Intracellular organisms in polymorphs in respiratory specimens can be visualized microscopically by a variety of staining methods. The quantification of such 'infected' cells has been proposed as a rapid method for the diagnosis of pneumonia and three recent cohort studies have compared this with other techniques. A study that compared quantitative cultures of mini-BAL specimens with the percentage of intracellular organisms in the same specimens found that a cut-off of >2% of infected cells gave a sensitivity of 80% and a specificity of 82%.²⁰⁷ A second trial determined that the sensitivity and specificity of infected cells in bronchoscopic BAL specimens with a cut-off of >1% was 93.6% and 91.5%, respectively.¹⁹⁸ In this study, the therapeutic plan was considered to be correct in only 65% of cases when using clinical judgment alone, but in 88% when guided by the microscopy results. Quantitative culture of BAL specimens has been described as having diagnostic sensitivities, specificities, positive predictive values, negative predictive values and correct classification (into pneumonia or not pneumonia) of 94%, 100% 100%, 90% and 96%, respectively.²⁰¹ Using quantification of intracellular organisms in the same specimens, with a culture cut-off point of $\geq 10^4$ cfu/mL, the values were 100%, 94%, 97%, 100% and 98%, respectively. Thus, in comparison with quantitative cultures, the detection of intracellular organisms in BAL specimens is a rapid specific test with high positive predictive value.

We recommend that quantification of intracellular organisms in BAL specimens is a rapid and specific test and can be used as a guide to initial therapy. Recommendation Grade A

4. Treatment

4.1. The prevention of HAP using antimicrobials

4.1.1. The role of selective decontamination of the digestive tract (SDD)

The use of systemic antibiotics alone or in conjunction with topically applied non-absorbable antibiotics as part of an SDD regimen has been investigated for the prevention of HAP, particularly VAP.

4.1.2. An assessment of the impact of SDD

Two recent systematic reviews,^{208,209} a recent meta-analysis²¹⁰ and a Cochrane review²¹¹ which consider the benefit of SDD in the prevention of HAP were reviewed. All of these demonstrate significant reductions in HAP or respiratory infection. One systematic review also demonstrated a significant reduction in overall mortality with SDD,²⁰⁹ whereas another showed a reduction in mortality in critically ill surgical patients only.²⁰⁸ The final systematic review found no significant mortality reduction.²¹⁰ However, the Cochrane review reported that a combination of topical and systemic prophylactic antibiotics reduces respiratory tract infections and overall mortality in adult patients receiving intensive care.²¹¹ A treatment based on the use of topical prophylaxis alone reduced respiratory infections but not mortality.²¹¹ A more recent meta-analysis examined the relationship between methodological trial quality and the effects of SDD and found that the better quality research papers, as defined by their scoring method, demonstrated less benefit in terms of pneumonia reduction, although a small but significant reduction in mortality was found in the high-quality studies.²¹² Five RCTs not included in these meta-analyses were also assessed and these were consistent with the above reported benefits from SDD.^{213–217}

Quantification of the potential beneficial impact of using SDD has been undertaken. A meta-analysis of 33 RCTs showed that the number of patients needing treatment (NNT) to prevent one case of VAP was 5 and to prevent one death was 23.²⁰⁹ The Cochrane review reported that on average, 5 patients needed to be treated with SDD to prevent one respiratory tract infection and 21 patients to prevent one death²¹¹ and the results from an RCT²¹³ as assessed by other workers²¹⁸ were consistent with an NNT to prevent one death of 12 patients.

There is thus evidence of benefit from SDD, consistently demonstrated across all patient groups, in the reduction of morbidity and mortality associated with VAP. There is also good evidence that a reduction in respiratory tract infections will affect mortality but, as the evidence is in critically ill patients with VAP, it is less clear how this translates to other forms of HAP. There is insufficient evidence to assess if particular patient subgroups benefit significantly over others.

We recommend that where it is anticipated that mechanical ventilation will be for ≥ 48 h, SDD should be considered for ICU patients in order to prevent the development of VAP. Recommendation Grade A

4.1.3. The choice of antimicrobial treatments for SDD

Two recent meta-analyses addressed the best methods of SDD.^{208,209} Both studies found that the greatest reduction in

respiratory infection were observed where both topical and systemic components of treatment were administered. A more recent RCT performed that used topical SDD alone demonstrated a significant reduction in VAP in patients receiving a modified SDD topical regimen (polymyxin, tobramycin and amphotericin). No difference in mortality in the two groups was found.²¹⁴ A wide range of choices and drug doses have been employed for SDD, but there is no available evidence as to which is the best regimen. With regard to duration of administration, most trials are consistent in using SDD throughout the ICU stay, with the systemic element being given for 3–4 days only, and subject to modification for the treatment of sepsis. Further research into SDD is needed to determine the best regimen and to identify the best selections of agents if units have particularly resistant organisms, e.g. MRSA, multidrug-resistant *Acinetobacter* spp. or extended-spectrum β -lactamase-producing organisms.

We recommend that SDD regimens should include topical and parenteral agents with activity against Gram-negative bacilli and that the choice of treatment should depend on local pathogen antimicrobial susceptibility profiles. Recommendation Grade A

4.1.4. *The relationship of resistance development to SDD*

A meta-analysis reported that the practice of SDD led to trends towards colonization in patients with Gram-positive organisms and pneumonia due to resistant Gram-positive organisms, but this effect was not statistically significant.²¹⁰ The Cochrane review found that there was no evidence of generalized emergence of resistance, with only isolated reports.²¹¹ An RCT described no change comparing SDD with conventionally managed patients in Gram-positive resistance though there was a reduction in Gram-negative resistance.²¹³ Although another RCT found an increase in Gram-positive organisms including MRSA in the group treated with SDD, this was felt to have been related possibly to a cross-infection problem.²¹⁵ Thus, there is an absence of evidence that use of SDD results in emergence and generalized spread of resistance, but isolated reports of such problems arising on units deploying SDD are described. In view of the emerging resistance patterns of the Gram-positive and Gram-negative bacteria currently encountered in UK hospitals, further research is required to assess the long-term effect of SDD on antimicrobial resistance and also to evaluate the effect of SDD on the development of *C. difficile* infection.

We recommend that the use of SDD should not be withheld because of concerns about the development of antibiotic resistance. Recommendation Grade A

We recommend that SDD requires to be supported by good infection control and planned prospective susceptibility surveillance in order that any problems can be identified early and addressed. Recommendation Grade GPP

4.1.5. *The cost-effectiveness of SDD*

SDD carries with it costs in respect of pharmacy and other opportunity costs as well as in the funds required to support a concomitant antimicrobial resistance surveillance activity. There are RCTs from Spain,^{216,219} France²²⁰ and Holland²²¹ that were structured to assess both clinical outcome and cost-effectiveness in relation to cost per survivor. As resource costs vary from

country to country, these studies cannot be assumed to apply to each nation either in terms of quantum or direction. However, all these four RCTs that have assessed costs per survivor have demonstrated that SDD is a cost-effective procedure.

We recommend that although initial expenditure to implement SDD may be higher than standard management, the use of SDD can be cost-effective in terms of individual cost per survivor. Recommendation Grade B

As costs vary between countries, we recommend that an estimate of local cost should be made for SDD protocols in each unit. Recommendation Grade GPP

4.1.6. *Prevention of HAP using parenteral antibiotic prophylaxis*

There is evidence from three RCTs that using systemic prophylaxis alone is beneficial in reducing the risks of VAP in ventilated patients with neurological trauma or burns.^{222–224} No assessment of the potential for resistance emergence was assessed in these studies. In the first, full treatment doses were used, whereas in the second, although a trend to reduction in mortality was shown, the study was underpowered to observe a significant difference. The final trial was the poorest in quality enrolling the least number of patients and in it the observers were not blinded to the treatment allocation. The magnitude of treatment effect from systemic antibiotic prophylaxis alone is less than that from SDD, and SDD is thus to be preferred. There are no good studies available on the relationship of modern surgical antibiotic prophylaxis practice to the development and outcome of HAP.

We recommend that systemic antibiotic prophylaxis alone should not be used in the prevention of HAP, but only as part of an SDD regimen. Recommendation Grade B

4.2. *Treatment with antimicrobials in the management of HAP*

There is a large body of evidence about the use of antimicrobials in the management of HAP from RCTs over the past three decades. However, several of the earlier studies evaluated antibiotics that are no longer regarded as appropriate empirical therapy of patients with HAP, particularly those with late-onset infections, owing to dramatic changes in the nature and susceptibility patterns of the pathogens currently recognized in most UK hospitals. Moreover, there are no well-conducted studies that have undertaken pharmaco-economic or health economic evaluations.

4.2.1. *Selection of antimicrobials in the management of HAP*

There are many limitations in the quality of the available evidence to assist in approaches to antimicrobial selection in HAP. Few studies have compared more than two therapeutic options and very few studies had sufficient power to demonstrate the superiority of one regimen over another. A further limitation is that the primary microbiological evaluations were invariably related to patients whose pathogens were susceptible to the trial antibiotics. Only six studies recruited 200 or more patients to both treatment and comparator arms.^{225–230} Only five studies were randomized double-blind studies.^{225,226,230–232} In several

studies, so, few patients were enrolled that the likelihood of a type II error is high.^{178,233–259} Finally, none of the studies addressed patient demography and risk factors or assessed empirical or definitive treatment in relation to severity of illness or duration of hospitalization. There are only a few studies that differentiate between Gram-positive^{225,226,231,260} and Gram-negative pathogens alone.^{233,245,250,254,255,257,261,262} Most studies looked at a mix of Gram-positive and -negative pathogens^{228–230,232,236,237,240,241,243,248,250,252–254,257,263–283} Several studies enrolled patients who were either ventilated or non-ventilated. Where the therapy was active against the pathogens, there were no differences between the groups in terms of assessed outcome whether clinical or microbiological. For all of the above reasons it is not possible to identify an optimal antibiotic regimen. However, although the pathogens and their susceptibility patterns associated with late-onset HAP are highly variable, those found in early-onset infections are few in number and remarkably consistent from centre to centre (see Section 3.4.1).

We recommend that the choice of empirical antibiotic therapy of patients with HAP in an individual unit should be based on the knowledge of the nature and susceptibility patterns of the pathogens that are prevalent on that unit and should also take account of such variables as duration of hospital stay (i.e. early- or late-onset infection), recent administration of antibiotic therapy and co-morbidities. Similarly, definitive therapy should be determined by culture and susceptibility test results. Recommendation Grade A

For patients with early-onset infections (fewer than 5 days following admission to hospital) who have not previously received antibiotics and in the absence of other risk factors, the use of co-amoxiclav or cefuroxime would be appropriate. Recommendation Grade GPP

For patients with early-onset infections (fewer than 5 days following admission to hospital) who have recently received antibiotics and/or who have other risk factors, a third-generation cephalosporin (cefotaxime or ceftriaxone), a fluoroquinolone or piperacillin/tazobactam would be appropriate. Recommendation Grade GPP

4.3. The role of invasive sampling and quantitative microbiology of respiratory secretions in directing antimicrobial therapy in HAP/VAP

As described above, invasive sampling and quantitative microbiology of respiratory secretions has a low specificity and sensitivity for the diagnosis of HAP/VAP. The use of these techniques for directing or modifying antibiotic therapy of suspected VAP is therefore controversial.^{284–287} Several studies have investigated whether treatment based on invasive and quantitative microbiology can improve patient outcome.

4.3.1. Non-randomized studies

A prospective, non-randomized cohort study²⁸⁸ of patients with and without diagnostic bronchoscopy (quantitative analysis of bronchoscopy-directed PSB or BAL specimens) found that in the bronchoscopy group, the durations of ventilation and ICU stay were similar but mortality was lower (18.5% versus 34.7%, $P < 0.03$). This study also reported that these bronchoscopy

patients received fewer antibiotics and were more likely to discontinue antibiotics. This finding was supported by a retrospective cohort study²⁸⁹ which demonstrated that management based on quantitative bronchoscopy rather than the CPIS, resulted in reduced antibiotic prescribing. However, in the former work, although physicians were more confident in their diagnosis of VAP after diagnostic bronchoscopy, antibiotics were discontinued in only 9 of 34 patients (26.5%) who had no growth from PSB or BAL samples.

4.3.2. Randomized studies

Four more rigorous randomized prospective studies of ICU patients with suspected VAP have been performed. These measured outcomes of management based on either (i) clinical assessment and microscopy and/or quantitative or non-quantitative cultures of EAs (clinical management) or (ii) microscopy and/or quantitative cultures of PSB or BAL specimens (invasive management). A large multicentre study involving 413 patients found invasive management to be significantly associated with fewer deaths at 14 days, earlier improvement of organ dysfunction and less antibiotic use. There was no difference in length of ICU stay, hospital stay or ventilation.²⁹⁰ In smaller studies involving 51,²⁹¹ 76²⁹² and 88²⁹³ patients, respectively, no difference in length of stay on ICU, length of ventilation or mortality was found. In addition, the last of these studies did not detect a difference in changes in antibiotic therapy.²⁹³

4.3.3. The effect of reporting antimicrobial susceptibilities of organisms cultured from respiratory tract secretions

It is widely assumed that treatment outcomes of HAP/VAP will be affected by the susceptibilities of the infecting organisms. However, there is limited evidence to confirm this in patients with VAP. This may be because of the difficulties of making a certain diagnosis of pneumonia and of identifying the causative pathogen. In addition, microbiological results may come too late to influence outcome²⁹⁴ and/or broad-spectrum empirical therapy is often used before the microbiological diagnosis is confirmed. Nevertheless, having an organism in a BAL specimen resistant to the empirical therapy has been independently associated with mortality.^{294,295}

Infections with (usually multiply resistant) *P. aeruginosa* or *Acinetobacter* spp. have been associated with a higher mortality than with other pathogens,²⁹⁶ but in a recent retrospective cohort study, VAP associated with *Acinetobacter baumannii* was not significantly associated with attributable mortality or increased length of ICU stay, whether or not the isolates were carbapenem-resistant.²⁹⁷ Another recent study where all patients were treated with timely and appropriate antimicrobial therapy showed no difference in outcome between patients with VAP associated with MRSA or methicillin-susceptible *S. aureus*.²⁹⁸

4.3.4. The effect of timely and appropriate antimicrobial therapy in HAP/VAP

There are data that demonstrate that the influence in VAP of a delay in starting appropriate therapy, or where there is initial inappropriate antibiotic therapy, is to increase mortality rates and the length of time patients spend on mechanical ventilation and in

hospital.^{190,256,293–295,299–304} However, many of these studies have poor design and, in some, differences have not been statistically different. Delays in instituting therapy or withholding therapy while awaiting culture results have been associated with increased mortality rates in two studies^{294,304} but not in one other.³⁰⁵ There are no studies investigating non-intubated HAP patients.

A study²⁹⁴ involving 132 ventilated patients with radiological and clinical evidence of VAP undertook quantitative culture of bronchoscopy-directed BAL specimens within 24 h of clinical/radiological diagnosis and positive BAL specimens were defined as those that contained $>10^4$ cfu/mL bacteria. Patients with a strong clinical suspicion of VAP had a high mortality rate, regardless of whether BAL cultures confirmed the clinical diagnosis. When the BAL-positive patients received antibiotic therapy appropriate for their cultures prior to bronchoscopy, mortality was 38%, compared with 91% ($P < 0.001$) if therapy was inappropriate and 60% if no treatment was given. When patients were changed from inadequate to adequate therapy based on the BAL results, their mortality was comparable to those who continued to receive inadequate therapy. Thus, even if quantitative microbiology of bronchoscopy-directed BAL specimens correctly identifies appropriate antimicrobial therapy, this information becomes available too late to influence survival.

We recommend that there is inadequate evidence to support the use of invasive and quantitative microbiology for the diagnosis and initial therapy to improve outcome of VAP in individual patients. Recommendation Grade C

We recommend that initial appropriate antibiotic therapy should be instituted as soon as VAP is suspected and should be based on local microbiological surveillance data. Recommendation Grade C

We recommend that initial therapy should not be delayed while awaiting microbiological results. Recommendation Grade C

4.3.5. The duration of antimicrobial treatment in the management of HAP

In a blinded, multicentre RCT, patients were treated with antibiotics for either 8 or 15 days for bacteriologically confirmed late-onset VAP and those who received the shorter duration treatment had no difference from their conventionally treated counterparts in terms of mortality, ICU stay or major clinical outcomes such as resolution of fever, white blood cell count and arterial oxygenation.³⁰⁶ The emergence of multiresistant pathogens was lower in those who received the 8 day course and their overall use of antibiotics was also lower.

We recommend that where patients respond to therapy, the routine duration of empirical therapy should be no longer than 8 days. Recommendation Grade C

We recommend that in order to reduce mortality and morbidity in patients with VAP, treatment with an appropriate antibiotic should be started as soon as possible. Recommendation Grade C

4.3.6. Definitive treatment when the causative organism is *P. aeruginosa*

Infection caused by *P. aeruginosa* is associated with a significantly higher incidence of treatment failure than those caused by

other organisms.^{230,274,275} Subgroup analysis of studies in which imipenem was one of the antibiotics evaluated has shown statistically increased incidences of treatment failure when compared with ceftazidime ($P = 0.0004$)^{243,272} or piperacillin/tazobactam ($P = 0.004$).²⁶⁸ A large double-blind study in which ciprofloxacin was compared with imipenem showed that there was no statistically significant difference between the two drugs in terms of the eradication of *P. aeruginosa* from patients with HAP, although, overall, according to both univariate analysis (CI difference 3.5% to 28.5%; $P = 0.021$) and multiple logistic regression analysis (OR 2.08, 95% CI 1.04–4.16; $P = 0.039$), ciprofloxacin was more effective in terms of clinical and bacteriological cure rates in patients with infections caused by Gram-negative bacilli other than *P. aeruginosa*.²³⁰ When compared with the combination of ceftazidime and tobramycin, the administration of meropenem has also been demonstrated to be associated with higher incidences of treatment failure in patients with HAP caused by *P. aeruginosa*, although, overall, the latter produced higher clinical and microbiological cure rates ($P = 0.04$ and 0.006, respectively).²⁷⁶

We recommend that there is no proven optimal antibiotic regimen for patients with HAP suspected or proven to be caused by *P. aeruginosa*. Treatment options include ceftazidime, ciprofloxacin, meropenem and piperacillin/tazobactam. Recommendation GPP

4.3.7. Definitive treatment when the causative organism is MRSA

The efficacies of two novel antibiotics have been evaluated as therapy of patients with infections caused specifically by Gram-positive bacteria, in particular MRSA: quinapristin/dalfopristin²⁶⁰ and linezolid²²⁶ versus vancomycin, and linezolid versus teicoplanin.²³² However, it is unlikely that any of these studies had sufficient power to demonstrate superiority. There were two retrospective analyses of the combined data from the two double-blind studies involving linezolid. The first concluded that linezolid was associated with higher survival ($P = 0.025$) and clinical cure ($P = 0.01$) rates than vancomycin in patients with HAP caused by MRSA.²²⁵ The second analysis in VAP patients showed increased survival ($P = 0.01$), bacterial eradication ($P = 0.001$) and clinical cure ($P = 0.001$) rates.³⁰⁷ However, although more than 1000 patients were evaluated in the two trials, only 160 of these actually had documented infection caused by MRSA.

We recommend that on the basis of the few published studies and the difficulty in interpreting results from subgroup analysis, no firm conclusion can be reached on the use of linezolid or a glycopeptide as optimal treatment of patients with HAP or VAP caused by MRSA. Recommendation Grade GPP

4.3.8. The role of pharmacokinetic (PK) and pharmacodynamic (PD) antibiotic features as a guide to treatment selection in HAP

There is only a small body of evidence available from three cohort studies on the role of PK/PD assessments in the management of pneumonia.^{308–310} However, these studies are retrospective theoretical modelling into antimicrobial management rather than prospective RCTs. Therefore, it is not reasonable or

appropriate to extrapolate the findings from this small number of studies to treatment of HAP as a whole. Prospective RCTs should be progressed to explore the value of PK and PD in guiding treatment choice in HAP.

We recommend that in the current state of knowledge, PK/PD modelling should not be used to guide treatment selections in HAP. Recommendation Grade D

4.3.9. *The choice between monotherapy and combination therapy in the treatment of HAP*

There are no systematic reviews directly relevant to this question. Sixteen RCTs have enrolled patients with HAP and compared patients receiving monotherapy (carbapenems, cephalosporins or ureidopenicillin) with those receiving combination therapy [cephalosporins, carbapenems or penicillins (azlocillin, carbenicillin, co-amoxiclav and ticarcillin) with an aminoglycoside].^{235,238,252,256-259,274-281,311,312} Of these, only two compared the same β -lactam with and without an aminoglycoside. From the above studies, there is no evidence that clinical or bacteriological response rates can be improved with combination therapy (cephalosporins, carbapenems or penicillins and an aminoglycoside). There is also no evidence that when used in combination with an aminoglycoside, one class of β -lactam (cephalosporins, carbapenems or penicillins) is more effective than the others in terms of clinical or bacteriological response rates. However, few studies were sufficiently powered to enable superiority to be detected. A systematic review has considered the evidence of monotherapy versus combination therapy in the treatment of non-neutropenic patients with serious infections including pneumonia and found these to be equivalent.³¹³ However, increased incidences of toxicity were observed in patients receiving combination therapy that included an aminoglycoside.

We recommend that, wherever possible, antimicrobial monotherapy is used for the management of bacterial HAP. Recommendation Grade A

4.3.10. *Airway administration of antimicrobials in the management of HAP*

PK studies³¹⁴⁻³¹⁶ have demonstrated that high concentrations of aminoglycosides are achieved in bronchial secretions when these drugs are administered by either instillation or nebulization via an ET tube. However, ceftazidime³¹⁶ and imipenem³¹⁴ achieved significantly higher concentrations when administered by instillation than by nebulization.

One RCT³¹⁷ evaluated the efficacy of an antibiotic (tobramycin) instilled via ET tubes in patients with VAP caused by Gram-negative bacteria and who were also receiving parenteral therapy. Compared with a placebo, the bacteriological cure rate was significantly higher in the study group. However, there was no significant difference between the groups in terms of the clinical cure rate. In the culture-positive population, the emergence of resistance did not occur more frequently in the study group when compared with the control group. Finally, there was no statistically significant difference between the groups in terms of the incidence of adverse reactions, with the exception of a higher frequency of supraventricular tachycardia among patients in the study group. The small sample size and the large

number of patients who could not be evaluated are major deficiencies of this study. In a second RCT, tobramycin or placebo was nebulized via ET tubes to patients with VAP; all of the patients were also treated with parenteral antibiotics. There were no statistically significant differences between the groups in terms of time to extubation or tolerability. This study suffers from a small sample size.²³² A systematic review of patients with CF has demonstrated that aerosolized antipseudomonal antibiotics are associated with a statistically significant reduction in the incidences of acute exacerbations.³¹⁸ The applicability of these findings to patients with VAP is uncertain, but is worthy of further study. The limitations of the existing published trials, together with the absence of other robust evidence, preclude any firm conclusions regarding the efficacy of topical antibiotics as adjunctive therapy in patients with VAP.

We recommend that as there is insufficient evidence that the administration of topical antibiotics as an adjunct to parenteral therapy is beneficial to patients with VAP, the routine implementation of this intervention is not warranted. Recommendation Grade D

If antibiotics are to be given by the ET route, instillation through an ET tube, as opposed to nebulization, is the preferred route of administration. Recommendation Grade GPP

4.3.11. *Switching from intravenous to oral antimicrobial therapy in the management of HAP*

There are three RCTs^{270,319,320} that assess the efficacy of switching from intravenous to oral therapy in the treatment of HAP. All the studies were designed to examine the comparator antibiotics rather than to specifically address the benefits of switching from intravenous to oral formulations. Each had low numbers of patients and were not powered to show differences between treatment, only comparisons. The study reports did not include definitive information on the criteria that were used to determine when to switch patients from intravenous to oral formulations. Hence, the available evidence is uninterpretable to determine when and how to switch between intravenous and oral therapy in HAP so no recommendation can be made. Further targeted research is required into this topic.

We recommend that as there is no established evidence upon which to base the conversion of intravenous to oral treatment in the management of HAP, these decisions must be taken on a case by case basis according to the therapeutic clinical response to treatment. Recommendation Grade D

4.4. *Therapeutic modalities other than antimicrobials in the management of HAP*

4.4.1. *Activated protein C*

There is one large, good quality RCT conducted in hospitalized patients with sepsis and organ failure comparing activated protein C with placebo. This study included 164 centres recruiting patients of which >90% received antibiotics in addition to trial therapy. The trial was stopped early following an interim analysis due to mortality benefits in the activated protein C treated group. The final mortality results were based on 1690 patients of whom 53% had pneumonia and demonstrated a 19.4% reduction in the relative risk of death ($P = 0.005$).³²¹ No breakdown of HAP or CAP was provided therefore this trial

cannot be considered as definitive proof of improvement in HAP outcomes with activated protein C. Nevertheless, it is considered highly likely that a substantial proportion of the pneumonias in this large trial were hospital-acquired. Further studies with activated protein C in patients with diagnosed HAP are required to confirm these general findings.

We recommend that patients with sepsis, organ failure and HAP should be considered for treatment with activated protein C according to the manufacturer's guidance for use. Recommendation Grade B

4.4.2. Granulocyte-colony stimulating factor (G-CSF)

A systematic review³²² and four RCTs^{323–326} have investigated the role of drugs to promote increased white blood cell production in immunocompetent patients with HAP. One study³²³ assessed safety only and two others cannot be used to draw conclusions as the patient numbers were very small.^{324,326} The remaining RCT assessed efficacy in 701 patients with acquired or NP, though no breakdown was provided of the distribution between these. The patients, in addition to antibiotic therapy, were randomized to treatment with G-CSF or placebo.³²⁵ The study demonstrated no improvement in mortality for pneumonia outcomes in terms of treatment with G-CSF or placebo. Therefore, the evidence shows that G-CSF is not beneficial in the treatment of HAP.

We recommend that patients with sepsis and HAP should not be treated with G-CSF. Recommendation Grade A

4.4.3. Physiotherapy

Chest physiotherapy is commonly used in patients with HAP. An RCT that assessed the effect of physiotherapy, in combination with positive-pressure breathing, on pneumonia outcomes evaluated 54 patients with clinically diagnosed pneumonia. No significant difference in outcomes (duration of fever, length of stay and mortality) was observed. No breakdown of acquired or NP was provided and no assessment of the power of the study to detect a difference was undertaken.³²⁷ There is, therefore, no evidence to support improved HAP outcomes with chest physiotherapy.

Chest physiotherapy cannot be recommended for the direct management of patients with HAP due to lack of evidence demonstrating improved outcomes. Recommendation Grade B

Chest physiotherapy may be of value to patients suffering from or at risk of HAP and it might be appropriate to consider it as a therapeutic option in this broader context. Recommendation Grade GPP

4.4.4. Steroids

The evidence assessing the effect of steroids on HAP is very limited. Two cohort studies were identified.^{328,329} One of these was a pilot study and the other was based on an outbreak of *Branhamella catarrhalis*. As neither of these studies is directly relevant to the issue of HAP, no assertive recommendation can be made.

We recommend that in the absence of clear evidence of its benefit, the routine use of steroids in the management of cases of HAP cannot be promoted. Recommendation Grade D

4.5. The use of clinical protocols for treating HAP

Most of the literature investigating the use of protocols in pneumonia is either focused on CAP or looks at the prevention and diagnosis of HAP rather than its treatment. The literature relating to the impact of guidelines/protocols on pneumonia has been extensively evaluated and reviewed.^{330,331} These reviews concluded that clinical guidelines/protocols, which outline a number of key interventions, can improve the delivery of antibiotics, procurement of microbiological tests and may improve clinical effectiveness. However, little information exists around which single intervention works and at what cost. It would seem plausible to hypothesize that on the basis of these studies, one may be able to draw some similarities with the management of HAP/VAP as data specific to this area is limited.

4.5.1. Clinical outcomes

An RCT employed a clinical protocol utilizing a modified CPIS of ≤ 6 to select patients at low risk of HAP who would be deemed suitable for early discontinuation (at 3 days) of empirical therapy for HAP.¹⁷⁸ It compared a standard duration and choice of therapy which was at the clinician's discretion to ciprofloxacin monotherapy. The results confirmed that early discontinuation of empirical therapy was not associated with increased mortality; had a shorter duration of both stay and cost and was associated with lower rates of antibiotic resistance and superinfection. It concluded that a protocol for empirical therapy that guided clinical decision about the duration of therapy based on the CPIS could improve economic and microbiological outcomes without compromising clinical effectiveness. However, the study was not blinded, was primarily in one centre, consisted of mostly elderly men with chronic underlying diseases and was biased by the fact that clinicians began to minimize antibiotic poly-pharmacy and the duration of the therapy in the comparator (standard treatment) arm as the study progressed. This study, therefore, requires validation in different populations and in more severe forms of HAP.

An uncontrolled before and after study examined the impact of VAP guidelines on the primary outcome of appropriateness of initial empirical antibiotic therapy as judged against a subsequent positive culture.¹⁹ The secondary study outcomes included duration of therapy, mortality, secondary episodes of VAP and the length of hospital stay. The study was imbalanced by significant differences in baseline prevalence of co-morbidities such as COPD, congestive cardiac failure and serum albumin and also in differences in other treatments (e.g. dialysis, sucralfate). Following the implementation of VAP guidelines, this study demonstrated improvements in the appropriateness of prescribing (48% to 94%, $P > 0.001$), a reduction in the duration of antibiotic therapy (14.8–8.6 days, $P > 0.001$) and in subsequent episodes of VAP (24% to 7.7%, $P = 0.03$). The study did not examine cost-effectiveness or any impact on microbiological outcomes. The poor design of the study and the non-comparability of the patient populations indicate that these data are insufficiently robust to definitively support the implementation of a VAP guideline to improve any of the outcomes defined.³³¹

4.5.2. Cost-effectiveness

An RCT in patients with VAP on a medical ICU has explored the relationship of a clinical protocol in respect of cost-effectiveness.³³² The active antibiotic discontinuation policy,

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which did not alter patient outcome or hospital stay, resulted in a 2 day reduction of antibiotic use with associated cost savings. A non-blinded RCT¹⁷⁸ investigated a protocol for empirical therapy for patients at low risk of HAP. It found that the protocol reduced each of the duration of unnecessary antibiotic therapy, the length of hospital stay and the cost while also reducing the incidence of superinfection and resistance.¹⁷⁸ Further well-designed, prospective, intervention studies are required to assess the impact of specific HAP/VAP guidelines or protocols on heterogeneous populations and in severe HAP/VAP.

We recommend that clinical guidelines or protocols for empirical therapy of HAP/VAP should be introduced in certain clinical settings, as they are able to improve economic and microbiological outcomes without compromising efficacy. Recommendation Grade C

5. Conclusions

The preparation of this guideline is just the first step. Without wide dissemination of these recommendations, with their implementation and audit, the work of the Group will have been in vain. There is little evidence available to support guideline introduction and the need for research in this area sits alongside the other gaps in our knowledge highlighted in this paper. From this further research and feedback will come new knowledge and it will be important that the content of this document is kept under review to ensure that it reflects the best available contemporary evidence.

Addendum

Since completion of the guidelines, several references^{33,46,128,150,151,322} have been updated on their Internet sites. The current listings are given for these publications. The BSAC published guidelines for the management of MRSA sepsis in 2006 that included comment upon hospital-acquired lower respiratory tract infections.³³³

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Transparency declarations

A. G. has received funds for speaking at a symposium organized on behalf of Wyeth Pharmaceuticals Ltd. R. S. has received

personal remuneration for speaking at an educational meeting organized by Wyeth. R. G. M. has received speaker honoraria from AstraZeneca and Wyeth. D. N. presently is a member of a number of UK and European Pharmaceutical Advisory boards (tigecycline, Wyeth; ceftobiprole, Janssen-Cilag; daptomycin, Novartis; linezolid, Pfizer; and OPT-80, Optimer). He has received honoraria to speak at meetings organized by Pfizer, Wyeth and Novartis. M. W. has received honoraria for consultancy work, financial support to attend meetings and research funding from AstraZeneca, Bayer, Genzyme, Nabriva, Pfizer, Vicuron and Wyeth. A. D. G. and M. S. have received funds for speaking at symposia organized on behalf of Wyeth and E. B. has received fees for speaking at a symposium sponsored by Novartis and for being a member of advisory panels for Chiron, Novartis and Janssen-Cilag. He has also received sponsorship from Chiron to attend a conference. J. A., A. K., G. F., P. D., J. C. and C. F. have none to declare.

Comment on the editorial process

This Working Party Report was put out for public consultation from December 2005 to February 2006 and amended in the light of comments received, prior to submission to *JAC*. This national consultation exercise involving major stakeholders and other interested parties or individuals replaced the *JAC*'s standard peer review process. After submission, the final review and decision-making process was undertaken by the Editor-in-Chief in consultation with another member of the Editorial Board, neither of whom are members of the Working Party.

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