

**British Society for Antimicrobial Chemotherapy
(BSAC)**

**Hospital Acquired
Pneumonia (HAP)
Considered Judgement**

Diagnosis Work Group

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Key to evidence grading

Levels of evidence	
1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well conducted meta-analyses, systematic reviews of RCTs or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High Quality systematic reviews of case-control or cohort or studies High quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal
2+	Well conducted case control of cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
3	Non-analytical studies, e.g. case reports, case series
4	Expert opinion
Grades of recommendation	
A	At least one meta-analysis, systematic review, or RCT rated 1++, 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+, directly applicable to the target population, and demonstrating overall consistency of results.
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; <i>or</i> Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; <i>or</i> Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; <i>or</i> Extrapolated evidence from studies rated as 2+
Good Practice Point	
GPP	Recommended best practice based on the clinical experience of the HAP Working Group

List of abbreviations

Term	Abbreviation
Acute Lung Injury	ALI
Acute (adult) Respiratory Distress Syndrome	ARDS
American Thoracic Society	ATS
Bronchoalveolar Lavage	BAL
Blinded Bronchial Sampling	BBS
British Society for Antimicrobial Chemotherapy	BSAC
Chest radiograph	CRX
Clinical Pulmonary Infection Score	CPIS
Community Acquired Pneumonia	CAP
Computed Axial Tomography	CT
Endotracheal Aspirate	EA
Fibre Optic Bronchoscopy	FOB
Hospital Acquired Pneumonia	HAP
Infected Cells in BAL	IC-BAL
Intensive Care Unit	ICU
Left Ventricular Failure	LVF
Magnetic Resonance	MR
Meticillin-resistant <i>Staphylococcus aureus</i>	MRSA
Meticillin-susceptible <i>Staphylococcus aureus</i>	MSSA
National Nosocomial Infections Surveillance System	NNISS
Positron Emission Tomography	PET
Protected Specimen Brush	PSB
Ventilator Associated Pneumonia	VAP

BASC	Considered Judgement form HAP Diagnosis Working Party
Question 1 – What are the clinical diagnostic criteria for hospital-acquired pneumonia (HAP)?	
Reviewers — Dr Alistair Gascoigne and Dr Paul Dilworth	
1. Volume of evidence:	
<p>There is one recent systematic review covering diagnostic tests for ventilator-associated pneumonia (VAP) that considered publications up to 1998.¹ All other evidence comprises cohort studies^{2,3} or consensus opinion⁴ and is based on historical review/expert opinion.</p> <p>The diagnostic sensitivity of clinical suspicion can be improved by taking account of the presence of the presence of fever (core temperature >38.3°C), blood leukocytosis (>10,000 per mm³) or leukopenia (<4,000 per mm³), purulent tracheal secretions, and the presence of a new and/or persistent infiltrate on Chest Radiograph; however, if all these criteria were to be required, the diagnostic specificity would be poor.¹</p> <p>Kirtland <i>et al.</i> (1997) compared immediate post-mortem histology in 39 patients who had been mechanically ventilated for approximately 14 days with five clinical diagnostic criteria (fever, leucocytosis, positive sputum culture, worsening chest radiograph changes and worsening gas exchange). None of clinical criteria or any combination of them correlated with the presence or absence of histological pneumonia.⁵</p> <p>The Clinical Pulmonary Infection Score (CPIS) is based on six criteria (the previous four - fever, leucocytosis, positive sputum culture and worsening chest radiograph changes - plus oxygenation (PaO₂/FiO₂) and semi-quantitative cultures of tracheal aspirates with or without Gram stain) and has been claimed to further increase sensitivity.^{6,7} In a prospective case series, Fàbregas <i>et al.</i> (1999) studied 25 deceased patients who had been mechanically ventilated before death.⁸ The presence of both histological pneumonia and positive lung cultures immediately post mortem was used as a reference test for VAP. In these patients CPIS was not superior to conventional clinical criteria for the diagnosis of VAP before death. Fartoukh <i>et al.</i> (2003) investigated the utility of a modified CPIS in a prospective cohort study. Conventional clinical diagnosis was inaccurate (sensitivity 50%, specificity 58%); CPIS was only slightly more accurate (sensitivity 60%, specificity 59%). Adding Gram stain results of Bronchoalveolar Lavages (BALs) slightly increased the accuracy of both conventional (sensitivity 85%, specificity 49%) and CPIS (sensitivity 78%, specificity 56%).³</p> <p>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. Luna <i>et al.</i> (2003) performed a prospective, multicenter cohort study of ventilated patients with suspected VAP. Serial measurements of CPIS were used to monitor the clinical course of VAP and identified patients with a good prognosis by day three.⁹ Singh <i>et al.</i> (2000)¹⁰ investigated patients with pulmonary infiltrates with suspected VAP but with a CPIS score of less than or equal to six (low likelihood of pneumonia); patients were randomised to receive standard therapy or ciprofloxacin monotherapy with discontinuation at day three if the CPIS remained less than or equal to six. 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.¹⁰</p>	

2. Applicability:
Most published evidence is based on studies of VAP, ^{1,11} whereas the majority of pneumonia in hospitals is HAP in non-intubated patients. Furthermore, most studies include only patients suspected of having HAP although some patients not thought to have HAP have been diagnosed at autopsy.
3. Generalisability:
The evidence is largely from VAP studies. This can be extrapolated pragmatically to non-intubated HAP patients. The assessment of diagnostic criteria is compromised by the lack of an agreed standard reference for identification of HAP. Clinical diagnostic criteria described in consensus opinion statements ^{4,12,13,14} 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 diagnosis of HAP often cannot be made on clinical criteria alone.
4. Consistency:
The evidence for the core clinical criteria of HAP is consistent. Patients presenting with core signs are likely to have some form of infection and require further clinical investigation.
5. Clinical impact:
HAP is associated with high rates of morbidity and mortality. Inaccurate diagnosis may result in patients with HAP not receiving antibiotics or those who do not have HAP receiving antibiotics unnecessarily. It is therefore essential to make a prompt and accurate diagnosis whenever possible and quickly implement the most appropriate management and treatment.
6. Other factors:
In order to simplify management and teaching, a pragmatic approach has been taken in the diagnosis of pneumonia taking account of previous clinical experience.

7. Evidence statement:	Evidence grading
There is a moderate amount of evidence comparing clinical diagnostic criteria with reference criteria, including histology. ¹	2-
There can be considerable variation in the clinical presentation of HAP, which is especially affected by the age of patient and the presence of co-morbidities. Distinction from other forms of sepsis may be difficult.	2-
In some patients increasing severity of pneumonia may be associated with increasing evidence of circulatory collapse (shock, tachycardia, hypotension and elevated blood urea concentrations). ^{15,16}	2-
However, it is not possible to generate a single event or series of events to define diagnostic criteria.	2+
CPIS is no better than general diagnostic criteria, but there is some evidence that it is useful in monitoring the response to therapy in VAP patients and selecting those for whom short-course treatment is appropriate.	2+

8. Recommendation:	
<p>The clinical diagnosis of HAP is difficult but can be based on the following criteria:</p> <ol style="list-style-type: none"> 1. New and/or persistent infiltrate on chest radiograph; 2. Core temperature >38.3 °C, secretions, and the presence of a Chest Radiograph change 3. Pyrexia – Temperature <36.0 °C or >38.3 °C 4. Purulent sputum in non-intubated patients or tracheal secretions in intubated patients 5. Blood leucocytosis (>12,000 per mm³) or leukopenia (<4,000 per mm³) 6. Increased inhaled oxygen requirement 7. Cough 8. Increased respiratory rate 9. Purulent tracheal secretions (Gram stain of BAL increases accuracy of diagnosis) 10. The patient may also exhibit confusion 11. Other organ failure 	C
<p>CPIS may be useful for selecting patients for short-course therapy and monitoring response to treatment.</p>	C

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5	Kirtland SH, Corley DE, Winterbaur RH <i>et al.</i> The diagnosis of ventilator-associated pneumonia: a comparison of histologic, microbiologic, and clinical criteria. <i>Chest</i> 1997; 112 : 445-57.
6	Pugin J, Auckenthaler R, Mili N <i>et al.</i> Diagnosis of ventilator-associated pneumonia by bacteriologic analysis of bronchoscopic and non-bronchoscopic “blind” bronchoalveolar lavage fluid. <i>Am Rev Respir Dis</i> 1991; 143 : 1121–9.
7	Pugin J: Clinical signs and scores for the diagnosis of ventilator-associated pneumonia. <i>Minerva Anestesiologica</i> 2002, 68 : 261-265.
8	Fàbregas N, Ewig S, Torres A <i>et al.</i> Clinical diagnosis of ventilator associated pneumonia revisited: comparative validation using immediate post-mortem lung biopsies. <i>Thorax</i> 1999; 54 : 867–73.

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BASC	Considered Judgement form HAP Diagnosis Working Party
Question 2 - Are there key differentiating imaging investigations that can establish the diagnosis of HAP?	
Reviewers — Dr Joanne Cleverly, Dr Alistair Gascoigne, and Dr Paul Dilworth	
1. Volume of evidence:	
<p>There is little available evidence to address this question. There is only one systematic review¹⁷ which with other reviews of diagnostic studies, focus on ventilator associated pneumonia (VAP).^{6,12,18,19,20}</p> <p>Publications on diagnostic imaging in VAP/HAP have been mainly limited to the use of Chest Radiographs (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 (see below) but, MR and PET have no demonstrated role.</p>	
2. Applicability:	
Existing work focuses on VAP, whereas most patients with or at risk of HAP are non-intubated.	
3. Generalisability:	
<p>The assessment of diagnostic criteria is compromised by the lack of an agreed standard reference for identification of HAP.</p> <p>A CXR has a vital role to play in diagnosing HAP in non-intubated patients, but is unhelpful for the diagnosis of VAP.</p>	
4. Consistency:	
The diagnostic value of radiographs is possibly greater in HAP than VAP, because of the problems of performing mobile Radiograph investigations on ventilated patients who cannot be moved, and because of the existing cardiothoracic co-morbidities often present in such patients.	
5. Clinical impact:	
Radiological investigations of patients with VAP do not often influence outcome. They are more useful in patients with HAP where they may provide information on differential diagnosis, complications or the exclusion of other pathology.	
6. Other factors:	
None.	

7. Evidence statement:	Evidence grading
There are no key imaging investigations that can establish the diagnosis of HAP, but a normal chest radiograph excludes HAP.	2++
The presence of an alveolar infiltrate on the CXR raises the possibility of HAP as well as other differential diagnoses.	2-
Ventilated patients may have abnormal chest radiographs secondary to other pathology such as acute lung injury, left ventricular failure, aspiration or alveolar haemorrhage, as well as infection. The presence of new infiltrates may indicate HAP.	2-
8. Recommendation:	
A good quality CXR should be obtained and compared with previous chest radiographs if available.	D
CT scanning may assist in the diagnosis and guide management in patients who are not responding to treatment and who have a complex chest radiograph.	GPP

References:	
6	Pugin J, Auckenthaler R, Mili N <i>et al.</i> Diagnosis of ventilator-associated pneumonia by bacteriologic analysis of bronchoscopic and non-bronchoscopic "blind" bronchoalveolar lavage fluid. <i>Am Rev Respir Dis</i> 1991; 143 : 1121-9.
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19	Garrard CS, A'Court CD. The diagnosis of pneumonia in the critically ill. <i>Chest</i> 1995; 108 Suppl 2: 17s-25s.
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BASC	Considered Judgement form HAP Diagnosis Working Party
Question 3 – What organisms are isolated from respiratory specimens in patients with suspected HAP?	
Reviewers — Prof Gary French and Dr Alistair Gascoigne	
1. Volume of evidence:	
<p>A wide range of bacteria is associated with HAP and VAP. The literature is extensive, consisting mainly of observational studies based on surveillance epidemiology.</p> <p>The most common organisms isolated from respiratory specimens of patients known or suspected to have HAP are <i>Pseudomonas aeruginosa</i>, <i>Staphylococcus aureus</i> and enterobacteria (especially <i>Klebsiella</i>, <i>E. coli</i> and <i>Enterobacter</i> spp.). Polymicrobial cultures are common in VAP, occurring in up to 60% of the case studies reviewed by Chastre & Fagon (2002).²¹ Anaerobes and fungi are uncommon.</p> <p>The longer a patient is in hospital the wider the spectrum of likely pathogens and the more likely they are to be multiply drug resistant. Resistance rates in nosocomial pathogens are increasing, particularly in intensive care units (ICUs).^{22,23} However, the relative frequency of organisms involved shows variation between geographical sites and dates of studies. (See Table 1 and Rello et al.(1999))²⁴. In recent years the prevalence of meticillin-resistant <i>Staphylococcus aureus</i>. (MRSA) and other multi-resistant organisms has been increasing,²⁵ especially in late-onset VAP.^{26,27}</p> <p>Most microbial surveillance studies have used invasive and/or quantitative microbiology (see <i>Question 5 - What is the best specimen for quantitative and qualitative microbiology of respiratory secretions?</i>) but there is no agreement on criteria to distinguish colonisation from infection and culture results should be interpreted with caution. A summary of the published data on respiratory isolates in HAP is shown in tables 1 and 2 below.</p> <p>Blood culture isolates that are not contaminants are generally regarded as significant pathogens that require treatment. However, in a prospective observational study of 162 ICU patients with evidence of VAP, Luna <i>et al</i> (1999) found that there was a poor correlation between organisms isolated from blood cultures and from Bronchoalveolar Lavages (BALs).²⁸ Bacteraemia was not associated with increased complications, length of stay, severity of illness or mortality. They concluded that organisms isolated from the blood are not necessarily those causing VAP.²⁸</p>	

Table 1. Frequency of organisms isolated from patients with suspected HAP in the US. National Nosocomial Infections Surveillance System (NNISS - 1985-1997), the European EPIC study (1992) and the Eole French study (2002)

Predominant Pathogens*	USA (NNISS)			Europe (EPIC)	France (Eole)
	a	a	b	c	d
Reference Year	1985-1988	1989	1992-1997	1992	1997-1998
Gram-negatives					
<i>Pseudomonas aeruginosa</i> /spp.	17.2	16	21	29.8	17
<i>E. coli</i> .	6.4	4	4	6.8	13
<i>Klebsiella</i> spp.	7.4	7	8	8.0	4
<i>Enterobacter</i> spp.	10.4	11	9	7.9	4
<i>Serratia</i> spp.	4.5		4		4
Other enterobacteria			4		
<i>Haemophilus influenzae</i>	6.4	5		10.2	19
<i>Acinetobacter</i> spp.		4	6	9.9	2
Gram-positives					
<i>Staphylococcus aureus</i>	14.6	20	20	31.7	27
Other staphylococci			1	10.6	7
<i>Streptococcus pneumoniae</i>					10
Other Streptococci					10
Enterococci			2		
Others					
<i>Candida albicans</i>		5	5	14.0	1 ('fungi', not specified)

a - Bergogne-Berezin E. (1995)²⁹

b - Richards MJ, Edwards JR, Culver DH, *et al.* (1999)³⁰

c - Vincent JL, Bihari DJ, Suter PM, *et al.* (1995)³¹

d - Montravers P, Veber B, Auboyer C *et al.* (2002)³²

Table 2: Distribution of organisms isolated from cases of ventilator-associated pneumonia by bronchoscopic techniques in 24 studies (1989-2000) including 1,689 episodes and 2,490 pathogens (from Chastre J, Fagon J-Y. 2002)²¹

Pathogen	Frequency (%)
<i>Pseudomonas aeruginosa</i>	24.4
<i>Acinetobacter</i> spp.	7.9
<i>Stenotrophomonas maltophilia</i>	1.7
Enterobacteriaceae*	14.1
<i>Haemophilus</i> spp.	9.8
<i>Staphylococcus aureus</i> [†]	20.4
<i>Streptococcus</i> spp.	8.0
<i>Streptococcus pneumoniae</i>	4.1
Coagulase-negative staphylococci	1.4
<i>Neisseria</i> spp.	2.6
Anaerobes	0.9
Fungi	0.9
Others (<1% each) [‡]	3.8

* Distribution 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%.

† Distribution when specified: methicillin-resistant *S. aureus*, 55.7%; methicillin-sensitive *S. aureus*, 44.3%.

‡ Including *Corynebacterium* spp., *Moraxella* spp., and *Enterococcus* spp.

2. Applicability:

In most reports there has been no distinction between organisms causing colonisation and those causing true infection and therefore published culture results should be interpreted with caution.

3. Generalisability:

Most studies have been performed in patients with VAP and this has been extrapolated pragmatically to HAP. In general, more resistant and more opportunistic organisms are isolated from patients with:

- Prior anti-microbial treatment
- Prolonged hospital stay
- Artificial ventilation
- Stay on Intensive Care Units (ICUs)

4. Consistency:

The evidence is consistent but evolving.

5. Clinical impact:

It is important to identify the causative organisms of HAP in order to direct antimicrobial therapy. In individual patients the true pathogen may not be isolated from respiratory specimens and bacteria that are cultured may be merely colonisers. However, accumulated local data on the distribution and susceptibilities of organisms isolated from patients with HAP are a useful guide to initial therapy.

6. Other factors:

Infection needs to be distinguished from colonisation but there are no defined criteria to do this.

7. Evidence statement:	Evidence grading
<p>Many organisms have been isolated from respiratory specimens of patients with HAP, predominantly aerobic bacteria and often in mixed culture, However, there are no agreed criteria to distinguish contamination, colonisation and infection. The distribution of isolates varies with time and place but the commonest species are <i>Pseudomonas aeruginosa</i>, enterobacteria and <i>Staphylococcus aureus</i>. In more recent studies <i>Staphylococcus aureus</i> isolates are often meticillin-resistant. Patients are more likely to have multi-resistant opportunistic organisms if they stay longer in hospital, have more intensive therapy and receive prior antimicrobial therapy.</p>	2+
8. Recommendation:	
<p>No direct evidence based recommendation can be made on microbiological surveillance data. Surveillance data, especially local data, should be used to guide therapy in potentially infected patients.</p>	-
<p>The significance of blood isolates should be reviewed in the light of the patients clinical condition during consultations between clinicians and microbiologists.</p>	GPP
<p>When likely (universally accepted) pathogens are isolated from respiratory specimens in patients with suspected HAP they should be treated.</p>	GPP
<p>The assessment of the causal aetiology of HAP should be guided by published national and international literature, local surveillance data and results of microbiological investigations in the individual patient.</p>	GPP
<p>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.</p>	GPP

References:

- | | |
|----|--|
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BASC	Considered Judgement form HAP Diagnosis Working Party
Question 4 – Is lung histology a suitable reference standard for the diagnosis of HAP?	
Reviewers — Prof Gary French, Dr Alistair Gascoigne	
1. Volume of evidence:	
<p>In an experimental baboon model of ventilated associated pneumonia (VAP), Johanson <i>et al.</i> assessed the severity of bronchopneumonia by lung histology.³³ Moderate/severe pneumonia was associated with high bacterial concentrations in homogenised lung tissue, and bacterial concentrations in BALs were linearly related to tissue values. This led to the concept that quantitative bacteriology of BAL or other deep respiratory specimen could be used for the accurate diagnosis of HAP/VAP. Many subsequent studies of lung biopsies in human patients have used lung histology as the reference standard for assessment of other diagnostic methods.</p> <p>In a prospective case study, by Corley <i>et al.</i> (1997), post mortem lung biopsies were performed less than one hour after death on 39 patients who had been mechanically ventilated for approximately 14 days.³⁴ Histological pneumonia was diagnosed by four independent pathologists in 7, 9, 12 and 15 cases (18-38%). One of the pathologists reviewed the slides blindly six months later and re-classified two patients (one previously diagnosed with and one previously diagnosed without pneumonia). A single pathologist then reviewed the slides by the Johanson criteria and diagnosed pneumonia in 14 (36%).³⁴</p> <p>In a prospective case study of quantitative microbiology and open lung biopsies of ventilated patients (Wermet <i>et al</i>, 1998), histological lesions of pneumonia and tissue concentrations of bacteria were unevenly distributed through the lung parenchyma.³⁵ 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 were obtained by Rouby <i>et al</i> (1989) and Marquette <i>et al.</i> (1995, 1996).^{36,37,38}</p>	
2. Applicability:	
Many studies have used lung histology as the reference standard for the assessment of other diagnostic tests. These reports must be interpreted in the light of the evidence reviewed here on the limitations of histological diagnosis.	
3. Generalisability:	
These results should be taken into account in the interpretation of results in all studies.	
4. Consistency:	
There is insufficient evidence to assess consistency.	
5. Clinical impact:	
Lung biopsies are impractical and risky, are rarely used for diagnosis of HAP, and are not recommended for this purpose. However, histology and cultures of homogenised lung tissue have been used to validate other diagnostic tests such as quantitative microbiology of respiratory specimens; this work should be assessed in the light of evidence that histology and lung parenchymal cultures may not be reliable.	

6. Other factors:
None.

7. Evidence statement:	Evidence grading
The recognition of histological pneumonia may vary among pathologists.	2+
Histological evidence of pneumonia and bacterial concentrations may vary throughout the pneumonic lung.	2+
8. Recommendation:	
Lung histology cannot be used as a gold/reference standard in the diagnosis of HAP.	D
Future research recommendation	
<p>When biopsy is used as the reference standard for other diagnostic methods in HAP, the histological criteria should be standardised.</p> <p>Reliable histological diagnosis of HAP or quantitation of bacterial lung tissue concentrations must be based on several specimens from different areas of the lung.</p> <p>Studies using histology or parenchymal cultures as the reference standard for assessment of other diagnostic criteria in HAP should be interpreted with caution.</p>	

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BASC	Considered Judgement form HAP Diagnosis Working Party
Question 5 - What is the best specimen for quantitative and qualitative microbiology of respiratory secretions?	
Reviewers — Dr Alistair Gascoigne and Dr Paul Dilworth	
1. Volume of evidence:	
<p>In order to obtain diagnostic respiratory specimens from HAP patients that more accurately reflect the bacterial burden within the lung, attempts have been made to collect deep specimens and protect them from contamination from upper respiratory flora. There are many papers that compare quantitative microbiological results on specimens obtained by a wide variety of bronchoscopically directed or blind techniques using a variety of collection methods. The most commonly analysed are bronchoalveolar lavage (BAL), protected specimen brush (PSB) and endotracheal aspirate (EA).</p> <p>Cook & Mandell (2000) reported a systematic review of reports published from 1985 to 1995 on the accuracy of EA cultures for the diagnosis of VAP.³⁹ Twelve papers were considered. The sensitivity and specificity of quantitative EA cultures varied widely (sensitivity 38 - 100%, and specificity 14 - 100%). Qualitative EA cultures had a high sensitivity, moderate positive-predictive value and high negative predictive value. The authors concluded that there was no evidence that EA cultures were reliable for the diagnosis of VAP.³⁹</p> <p>Campbell (2000) presented a systematic review of studies up to 1998 of blinded bronchial sampling (BBS), mini-BAL and blinded sampling with PSB for the diagnosis of VAP.⁴⁰ Fifteen papers were considered. Diagnostic accuracy was similar to those of other fibre optic bronchoscopy (FOB) methods and side effects were also similar.⁴⁰</p> <p>Baughman (2000) reported a systematic review of PSB⁴¹ and Torres & El-Ebiary (2000) a similar review of BAL analysing papers up to 1998.⁴² de Jaeger <i>et al.</i> (1999)⁴³ conducted a high quality meta-analysis (reviewing papers up to the end of end of 1994) to compare the diagnostic value of quantitative cultures of respiratory secretions collected with PSB or BAL and the percentage of infected cells in BAL (IC-BAL). Twenty six papers were considered. They concluded that there was no significant difference between the diagnostic accuracy of PSB, BAL, and IC-BAL.⁴³ The results for IC-BAL were supported by a more recent prospective case study by Sirvent <i>et al.</i> (2003).⁴⁴ More recent prospective case studies have also found no differences between different methods. Wood <i>et al.</i> (2003) found no significant difference between the use of blind EA, bronchoscopic PSB, blinded PSB and BAL⁴⁵ and Mentec <i>et al.</i> (2004) no difference with blind EA, blind and directed protected telescoping catheter and BAL.⁴⁶ In patients with HAP there is good repeatability and correlation in the qualitative isolates in BAL but not when quantitative analysis is performed.⁴⁷</p> <p>While current opinion is to lavage from one lung there is clinical evidence that this may not be appropriate and bilateral lavage may be necessary on occasion.⁴⁸</p>	
2. Applicability:	
Most evidence is based on studies of VAP. The systematic and consensus reviews discuss the extrapolation to HAP in general.	

3. Generalisability:
These sampling methods have been assessed in VAP patients. The results can be extrapolated pragmatically to intubated HAP patients but the methods cannot be used in non-intubated patients.
4. Consistency:
The evidence of the relative effectiveness of the different techniques is consistent.
5. Clinical impact:
The choice of method has no specific impact on clinical outcome.
6. Other factors:
None.

7. Evidence statement:	Evidence grading
EA cultures are unreliable for the diagnosis of VAP.	1+
Blinded sampling techniques produce similar results to other fibre optic bronchoscopy (FOB) methods with no greater incidence of side effects.	1+
There is no significant difference between the diagnostic accuracy of PSB, BAL, and IC-BAL.	1+
8. Recommendation:	
There is a lack of evidence to indicate that any one method is better than the other.	A
EA cultures are not recommended for diagnosis of VAP.	A
There is no evidence that any one invasive sampling method is better than another. Therefore, the least expensive and least invasive technique requiring minimal expertise and allowing rapid implementation is recommended, for example, blind lavage. In addition, with BAL an immediate diagnostic result is available for IC-BAL pending BAL culture.	GPP

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BASC	Considered Judgement form HAP Diagnosis Working Party
Question 6 – Can quantitative and qualitative microbiology aid the diagnosis of HAP/VAP?	
Reviewers — Dr Alistair Gascoigne and Dr Paul Dilworth	
1. Volume of evidence:	
<p>A large amount of data assessing the diagnostic accuracy of quantitative microbiology has been published; however 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. None of these reference standards are reliable. A wide variety of invasive sampling techniques and quantitative microbiological criteria (cut off points) have been used, but the question regarding which specimen is best for microbiological assessment of respiratory secretions in this guideline shows that they all produce similar results (see <i>Question 5 - What is the best specimen for quantitative and qualitative microbiology of respiratory secretions?</i>).</p> <p>A systematic review of the use of quantitative microbiology for the diagnosis of hospital acquired pneumonia (HAP) / ventilator associated pneumonia (VAP) was published in a supplement to Chest with Baughman (2000) reviewing protected specimen brush (PSB)⁴¹ and Torres & El-Ebiary bronchoalveolar lavage (BAL)⁴². A meta-analysis comparing diagnostic methods is also relevant.⁴³ There are three consensus reviews^{4,12,49} and recent good quality general reviews by Baughman (2003),⁴¹ Ewig & Torres (2002),⁵⁰ Chastre & Fagon (2002)²¹ and the American Thoracic Society (ATS) (2005).¹⁴</p> <p>In the systematic review by Torres & El-Ebiary (2000),⁴² 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 detection of intracellular organisms in BAL specimens was found to be a rapid specific test with high positive predictive value. The other reviews have similar findings. However, the ATS guideline (2005) concluded that negative lower respiratory tract cultures in patients with no recent change in antibiotic therapy is an indication for stopping antibiotics (their evidence level 'moderate').¹⁴</p>	
2. Applicability:	
Most evidence is based on studies of VAP. The evidence from VAP can be extrapolated pragmatically to non-intubated HAP.	
3. Generalisability:	
The reviews address the difficulties of the clinical and investigational diagnosis of VAP and the meta-analysis by de Jaeger <i>et al</i> (2000) reviews the problems of using post-mortem histology as the reference standard. ⁴³ This latter issue is also addressed in this guideline in <i>Question 4 – Is lung histology a suitable reference standard for the diagnosis of HAP?</i>	
4. Consistency:	
The studies are consistent in that different studies have consistently reported a wide range of accuracy of microbiological diagnosis.	

5. Clinical impact:

There is a lack of evidence on the applicability of these tests to non-intubated HAP patients.

6. Other factors:

There is a bias in the available evidence in that clinical practice is already influenced by published studies on invasive microbiological techniques in ventilated patients. However, most patients with HAP - or in hospital and at risk of HAP - are not ventilated.

7. Evidence statement:**Evidence grading**

Quantitative microbiological investigations such as BAL 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.

1++

The detection of intracellular organisms in BAL specimens is a rapid test with high specificity.

1++**8. Recommendation:**

Quantitative microbiology should not be relied on for the diagnosis of HAP/VAP.

A

Blind lavage is recommended as a simple and effective method to obtain respiratory specimens and to identify potential pathogens in suspected HAP/VAP.

A

Identification of intracellular organisms in BAL specimens is a rapid and specific test and is recommended as a guide to therapy.

A**References:**

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BASC	Considered Judgement form HAP Diagnosis Working Party
Question 7 – Should invasive and quantitative microbiological results be used to direct therapy of HAP/VAP?	
Reviewers — Prof Gary French and Dr Alistair Gascoigne	
1. Volume of evidence:	
<p>Invasive sampling and quantitative microbiology has a low specificity and sensitivity for the diagnosis of hospital acquired pneumonia (HAP) (see <i>Question 6 – Can quantitative and qualitative microbiology aid the diagnosis of HAP/VAP?</i>). Its use as a method for direction or modification of therapy of suspected ventilator associated pneumonia (VAP) is controversial.^{51,52,53,54} Several studies have now been performed to investigate whether treatment based on invasive and quantitative microbiology can improve patient outcome.</p> <p>Four randomised prospective studies on intensive care unit (ICU) patients with suspected VAP measured outcomes with management based on either clinical assessment and microscopy and qualitative cultures of endotracheal aspirates (EAs) (clinical management), or microscopy and quantitative cultures of protected specimen brush (PSBs) or bronchoalveolar lavages (BALs) (invasive management). Fagon et al (2000) 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.⁵⁵ Sanchez-Nieto et al (1998), Ruiz et al. (2000) and Solé Violán et al (2000) found no difference in length of stay on ICU, length of ventilation or mortality.^{56,57,58} In addition, Solé Violán et al (2000) found no difference in changes in antibiotic therapy.⁵⁸</p> <p>Heyland et al (1999) conducted a prospective, non-randomised cohort study of patients with and without diagnostic bronchoscopy. In the bronchoscopy group, durations of ventilation and ICU stay were similar but mortality was lower (18.5% versus 34.7%, $p < 0.03$) and patients received fewer antibiotics and were more likely to discontinue antibiotics.⁵⁹ This is further supported by Luyt who demonstrated in a retrospective cohort study that quantitative bronchoscopy compared to Chronic Pulmonary Infection Score (CPIS) reduces antibiotic prescribing.⁶⁰</p> <p>It is widely assumed that treatment outcomes may 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 and of identifying the causative pathogen, and because broad spectrum empirical therapy is often used before the microbiological diagnosis is confirmed.</p> <p>Nevertheless, having an organism in a BAL specimen resistant to the empirical therapy has been independently associated with mortality.⁶¹ Infections with (usually multiply resistant) <i>Pseudomonas aeruginosa</i> or <i>Acinetobacter</i> spp. have been associated with a higher mortality than with other pathogens,⁶² but in a more recent retrospective cohort study, VAP associated with <i>A. baumannii</i> was not significantly associated with attributable mortality or increased length of ICU stay, whether or not the isolates were carbapenem resistant.⁶³ Another recent study showed no difference in outcome between patients with VAP associated with methicillin-resistant <i>Staphylococcus aureus</i> (MRSA) or methicillin-susceptible</p>	

Staphylococcus aureus (MSSA),⁶⁴ but all patients were treated with timely and appropriate antimicrobial therapy.

However, there is evidence that timely and appropriate antimicrobial therapy is associated with improved mortality rates in patients with suspected VAP,^{58,65,66,67,68,69,70} although 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 has been associated with increased mortality rates in two studies^{68,71} but not in one other.⁷² In the study by Iregui *et al.* (2002),⁷¹ all patients eventually received appropriate antimicrobial therapy, but in one group the treatment was delayed more a mean of approximately 29 hours compared with approximately 6 hours in the other. This delay was independently associated with increased mortality (adjusted odds ratio 7.68, $p < 0.001$).⁷¹

2. Applicability:

The evidence is applicable only to VAP or intubated patients with HAP.

3. Generalisability:

The evidence is applicable only to VAP or intubated patients with HAP.

4. Consistency:

The evidence is generally consistent but evolving.

5. Clinical impact:

The choice and timing of antimicrobial therapy has a significant impact on clinical outcomes.

6. Other factors:

None.

7. Evidence statement:	Evidence grading
There are no studies investigating non-intubated HAP patients.	-
There is conflicting evidence as to whether the use of invasive and quantitative microbiology to diagnose VAP and direct therapy is associated with improved outcomes.	1-
Timely and appropriate therapy for VAP based on local historical microbiological surveillance data is associated with reduced mortality.	1-
Delay in therapy while awaiting the results of microbiology is associated with increased mortality in VAP patients.	1-
There is some evidence that microbiological results in individual patients can be used to reduce or stop antimicrobial therapy (de-escalation) without worsening outcomes in VAP patients.	2++
8. Recommendation:	
All recommendations are based on VAP data. There is no evidence base to make recommendations on non-intubated HAP patients.	-

There is inadequate evidence to support the use of invasive and quantitative microbiology for diagnosis and initial therapy to improve outcome of VAP in individual patients.	C
Initial appropriate therapy should be instituted as soon as VAP is suspected and should be based on local microbiological surveillance data.	C
Initial therapy should not be delayed while awaiting microbiological results.	C

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