

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

**Hospital Acquired
Pneumonia (HAP)
Considered Judgement
Treatment Work Group**

Working Party Chair

Dr Robert Masterton

Treatment Group Chair

Dr Martin Street

Members

Dr Erwin Brown
Dr Angela Galloway
Prof Alan Knox
Dr Robert Masterton
Prof Dilip Nathwani
Prof Mark Wilcox

Prepared by: **corvus communications ltd**
On Track
Limes Lane
Buxted
East Sussex TN22 4PB
UK
Tel: +44(0)1825 733057
Fax: +44(0)1825 732065
Email: corvus@corvuscom.com

CONTENTS

Key to evidence grading	3
List of abbreviations	4
Question 1 - Is there any evidence of:	5
a. benefit from the practice of Selective Digestive Tract Decontamination (SDD)?	5
b. the best method of Selective Digestive Tract Decontamination (SDD)?	8
c. the disadvantages of Selective Digestive Tract Decontamination (SDD)?.....	10
d. Selective Digestive Tract Decontamination (SDD) is cost effective?	12
Question 2 - Is there any evidence of benefit from the use of prophylactic parenteral antibiotics in:	14
a. 'at-risk' patients?	14
b. perioperative surgical prophylaxis?	16
Question 6 - What are the optimal empirical and definitive antibiotic therapies of patients with HAP?	17
Question 7 - Is there any evidence that antibiotic treatment protocols for HAP are effective or cost effective?	26
Question 9 – Is there evidence to suggest that the pharmacodynamic and pharmacokinetic profiles of different antibiotics are important in selecting therapy/regimens or in influencing outcome?	29
Question 10 – Is there evidence of differing outcomes based on whether monotherapy or combination therapy is used and does this depend upon selected antibiotic classes?	31
Question 11 - Are data available to support the efficacy of instilled or nebulised therapy as an adjunct to standard therapy?	34
Question 12 – Are there clear criteria available for the initiation of step down therapy e.g. intravenous to oral?	37
Question 15 - What other treatment modalities are important in the management of HAP?	39
a. Activated Protein C.....	39
b. Granulocyte-Colony Stimulating Factor (G-CSF)	41
c. physiotherapy	43
d. steroids.....	44
References	45

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
British Society for Antimicrobial Chemotherapy	BSAC
Bronchoalveolar Lavage	BAL
Community Acquired Pneumonia	CAP
Congestive Cardiac Failure	CCF
Chronic Obstructive Pulmonary Disease	COPD
Clinical Pulmonary Infection Score	CPIS
Epithelial Lining Fluid	ELF
Endotracheal	ET
Granulocyte-Colony Stimulating Factor	G-CSF
Hospital Acquired Pneumonia	HAP
Intensive Care Unit	ICU
Intention to Treat	ITT
Meticillin-resistant <i>Staphylococcus aureus</i>	MRSA
Number of Patients Needed to be Treated	NNT
Pharmacodynamic	PD
Pharmacokinetic	PK
Randomised Controlled Trials	RCTs
Selective Digestive Tract Decontamination	SDD
Trimethoprim-sulfamethoxazole	TMP-SMX
Ventilator Associated Pneumonia	VAP

BSAC	Considered Judgement form HAP Treatment Working Party
<p>Question 1 - Is there any evidence of:</p> <p>a. benefit from the practice of Selective Digestive Tract Decontamination (SDD)?</p>	
<p>Reviewers — Dr Robert Masterton and Dr Angela Galloway</p>	
<p>1. Volume of evidence:</p>	
<p>Three recent systematic reviews^{1,2,3} and a Cochrane review⁴ which consider the benefit of SDD in the prevention of HAP were reviewed. All of these demonstrate significant reductions in hospital acquired pneumonia or respiratory infection. D'Amico also demonstrated a significant reduction in overall mortality with SDD.² Nathans demonstrated a reduction in mortality in the critically ill surgical patients only¹ though Kollef found no significant mortality reduction.³ 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. A treatment based on the use of topical prophylaxis alone reduces respiratory infections but not mortality.⁴ There was another earlier systematic review and meta-analysis published but they used less selective criteria for patient selection and covered older studies.^{5,6}</p>	
<p>A more recent meta-analysis by van Nieuwenhoven <i>et al.</i> 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 high quality studies.⁷</p>	
<p>The potential beneficial impact of using SDD has been shown by D'Amico² in a meta-analysis of 33 randomised controlled trials (RCTs). They showed that the number of patients needed to be treated (NNT) to prevent one case of Ventilator Associated Pneumonia (VAP) was five and to prevent one death was 23. The Cochrane review reported that on average five patients needed to be treated with SDD to prevent one respiratory tract infection and 21 patients to prevent one death⁴ and the results from an RCT by Kreuger <i>et al.</i> (2002)⁸ are consistent with an NNT to prevent one death was 12 as assessed by Filos (2003).⁹</p>	
<p>Five RCTs not included in these meta-analyses were also assessed.^{8,10,11,12,13} Krueger demonstrated a significant reduction in pneumonia ($p=0.007$) and other lower respiratory tract infections ($p=0.007$) in the SDD group but mortality was only significantly reduced for 237 patients ($p=0.0147$) who were in the mid range stratum (APACHE II score 20-29 on admission to ICU).⁸ De Jonge observed significant reductions in mortality (15% versus 23% for control $p=0.002$) and reduced colonisation with resistant Gram negative bacteria ($p=0.001$) in intensive care unit (ICU) patients (466 receiving SDD versus 468 controls).¹⁰ Nardi observed a significant reduction in VAP ($p=0.02$) in a single centre study using topical SDD treatment alone with 104 patients receiving a classical SDD topical regime versus 119 patients who received a modified regime with the addition of topical mupiricin.¹¹ Lingnau did not observe a significant reduction in HAP in ICU ventilated patients ($p=0.50$ pneumonia greater than 48 hours in the intention to treat patient (ITT) group). The number of patients recruited into this trial were: 198 patients in time period one (12 months preceding SDD in a prospective consecutive study); 310 patients receiving SDD versus 148 placebo in time period two (54 months during which a double blind, randomised and placebo controlled trial of SDD in ventilated patients was performed).¹² Conversely Sanchez observed significant reduction ($p<0.001$) in VAP in patients receiving SDD undergoing emergency surgery (131 SDD patients versus 140 controls).¹³</p>	

2. Applicability:
Fully
3. Generalisability:
Specific to ICU patients ventilated for more than 24 hours. The available evidence does not permit sub-set analysis according to severity of underlying illness, clinical background of patients or early versus late VAP.
4. Consistency:
Highly consistent.
5. Clinical impact:
There is a significant clinical impact demonstrated for morbidity and mortality.
6. Other factors:
Pharmacy and other opportunity costs and resource implications need to be considered. In addition SDD programmes require concomitant antimicrobial resistance surveillance activity.

7. Evidence statement:	Evidence grading
There is evidence of benefit, consistently demonstrated across all patient groups, in the reduction of morbidity and mortality, associated with VAP. There is 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 sub groups benefit significantly over others.	1++
8. Recommendation:	
Where it is anticipated that mechanical ventilation will be for longer than 24 hours SDD should be considered for ICU patients in order to prevent the development of VAP.	A
Consideration should be given to the endemic resistance profile of pathogens in the local unit. Choice of treatment should then be tailored to these local pathogen profiles.	GPP

References:	
1	WY784. Nathens AB, Marshall JC. Selective decontamination of the digestive tract in surgical patients: a systematic review of the evidence. <i>Arch Surg</i> 1999; 134 : 170-6.
2	WY627. D'Amico R, Pifferi S, Leonetti C <i>et al</i> . Effectiveness of antibiotic prophylaxis in critically ill adult patients: systematic review of randomised controlled trials. <i>BMJ</i> 1998; 316 : 1275-85.
3	WY778. Kollef MH. The role of selective digestive tract decontamination on mortality and respiratory tract infections. A meta-analysis. <i>Chest</i> 1994; 105 : 1101-8.
4	WY946. Liberati A, D'Amico R, Pifferi <i>et al</i> . Antibiotic prophylaxis to reduce respiratory tract infections and mortality in adults receiving intensive care. <i>The Cochrane Database</i>

- of Systematic Reviews* 2004, Issue 1. Art. No.: CD000022. DOI: 10.1002/14651858.CD000022.pub2.
- 5 WY942. Heyland DK, Cook DJ, Jaeschke R, *et al.* Selective decontamination of the digestive tract. An overview. *Chest* 1994; **105**: 1221-9.
 - 6 WY941. Selective Decontamination of the Digestive Tract Trialists' Collaborative Group. Meta-analysis of randomised controlled trials of selective decontamination of the digestive tract. *BMJ* 1993; **307**: 525-32.
 - 7 WY772. van Nieuwenhoven CA, Buskens E, van Tiel FH *et al.* Relationship between methodological trial quality and the effects of selective digestive decontamination on pneumonia and mortality in critically ill patients. *JAMA* 2001; **286**: 335-40.
 - 8 WY1600. Krueger WA, Lenhart FP, Neeser G *et al.* Influence of combined intravenous and topical antibiotic prophylaxis on the incidence of infections, organ dysfunctions and mortality in critically ill surgical patients: A prospective, stratified, randomised, double-blind, placebo-controlled clinical trial. *Am J Respir Crit Care Med* 2002; **166**: 1029-37.
 - 9 WY764. Filos KS. Selective decontamination of the digestive tract: Implications for the critically ill patient. A critical review. *Archives of Hellenic Medicine* 2003; **20** Suppl A: 78-86.
 - 10 WY763. de Jonge E, Schultz MJ, Spanjaard L *et al.* Effects of selective decontamination of digestive tract on mortality and acquisition of resistant bacteria in intensive care: a randomised controlled trial. *Lancet* 2003; **362**: 1011-16.
 - 11 WY769. Nardi G, Di Silvestre AD, De Monte A *et al.* Reduction in Gram-positive pneumonia and antibiotic consumption following the use of a SDD protocol including nasal and oral mupirocin. *Eur J Emerg Med* 2001; **8**: 203-14.
 - 12 WY775. Lingnau W, Berger J, Javorsky F *et al.* Changing bacterial ecology during a five-year period of selective intestinal decontamination. *J Hosp Infect* 1998; **39**: 195-206.
 - 13 WY1450. Sanchez GM, Cambronero Galache JA, Lopez DJ *et al.* Effectiveness and cost of selective decontamination of the digestive tract in critically ill intubated patients. A randomized, double-blind, placebo-controlled, multicenter trial. *Am J Respir Crit Care Med* 1998; **158**: 908-16.

BSAC	Considered Judgement form HAP Treatment Working Party
Question 1 continued	
Is there any evidence of:	
b. the best method of Selective Digestive Tract Decontamination (SDD)?	
Reviewers — Dr Robert Masterton and Dr Angela Galloway	
1. Volume of evidence:	
Two recent meta-analyses, one by Nathens and Marshall and the other by D'Amico <i>et al.</i> addressed the best methods of SDD. ^{1,2} Both studies found that the greatest reduction in respiratory infection were observed in studies where both topical and systemic components of treatment were considered. A more recent randomised controlled trial (RCT) performed by Nardi <i>et al.</i> using topical SDD alone, demonstrated a significant reduction in VAP in patients receiving a modified SDD topical regime (polymyxin, tobramycin and amphotericin). No difference in mortality in the two groups was found. ¹¹	
2. Applicability:	
Fully	
3. Generalisability:	
Specific to intensive care unit (ICU) patients ventilated for more than 24 hours.	
4. Consistency:	
Highly consistent.	
5. Clinical impact:	
There is a significant clinical impact demonstrated for morbidity and mortality.	
6. Other factors:	
Pharmacy and other opportunity costs and resource implications need to be considered. In additional SDD programmes require concomitant antimicrobial resistance surveillance activity.	
7. Evidence statement:	Evidence grading
There is good evidence that SDD needs to consist of topical and parenteral agents (with activity against aerobic Gram negative bacilli), but there is a lack of good evidence to indicate which particular regimens should be implemented. Regimens must address local pathogen profiles.	1+
8. Recommendation:	
SDD regimens should include topical and parenteral agents (with activity against Gram negative bacilli), and the choice of treatment should depend on local pathogen profiles.	A
References:	
1 WY784. Nathens AB, Marshall JC. Selective decontamination of the digestive tract in surgical patients: a systematic review of the evidence. <i>Arch Surg</i> 1999; 134 : 170-6.	

- 2 WY627. D'Amico R, Pifferi S, Leonetti C *et al.* Effectiveness of antibiotic prophylaxis in critically ill adult patients: systematic review of randomised controlled trials. *BMJ* 1998; **316**: 1275-85.
- 11 WY769. Nardi G, Di Silvestre AD, De Monte A *et al.* Reduction in Gram-positive pneumonia and antibiotic consumption following the use of a SDD protocol including nasal and oral mupirocin. *Eur J Emerg Med* 2001; **8**: 203-14.

BSAC	Considered Judgement form HAP Treatment Working Party
Question 1 continued	
Is there any evidence of: c. the disadvantages of Selective Digestive Tract Decontamination (SDD)?	
Reviewers — Dr Robert Masterton and Dr Angela Galloway	
1. Volume of evidence:	
Kollef's meta-analysis reported that the practice of SDD led to trends towards colonisation in patients with Gram positive organisms and pneumonia due to resistant Gram positive organisms but was not statistically significant. ³ In the recent Cochrane Review, there was no evidence of generalised emergence of resistance with only isolated single reports. ⁴ The randomised controlled trial (RCT) of de Jonge found no change in Gram positive resistance despite a reduction in Gram negative resistance with SDD. ¹⁰ Lingau and colleagues in 1998 found an increase in Gram positive organisms including methicillin-resistant <i>Staphylococcus aureus</i> (MRSA) in the group treated with SDD although this may have been related to a cross-infection problem. ¹²	
2. Applicability:	
Fully	
3. Generalisability:	
Specific to intensive care unit (ICU) patients ventilated for more than 24 hours.	
4. Consistency:	
Highly consistent.	
5. Clinical impact:	
There is a significant clinical impact demonstrated for morbidity and mortality.	
6. Other factors:	
Pharmacy and other opportunity costs and resource implications need to be considered. In addition SDD programmes require surveillance activity and good infection control practices.	

7. Evidence statement:	Evidence grading
There is an absence of evidence that use of SDD results in generalised spread of resistance. In the comprehensive Cochrane review there was no evidence of resistance emergence only isolated single reports.	1++
8. Recommendation:	
Use of SDD should not be withheld because of any concerns of resistance developing.	A
SDD requires to be supported by planned prospective susceptibility surveillance and good infection control.	GPP

Future Research Recommendations

Further studies are required to assess the effect of SDD compared with planned prospective susceptibility and pathogen surveillance and good infection control measures alone in preventing HAP.

Further studies on the effect of SDD on antimicrobial resistance need to be performed in view of the emerging resistance of Gram positive and Gram negative bacteria which are currently encountered in UK hospitals.

The effect of SDD on the development of *Clostridium difficile* infections also needs to be assessed.

References:

- 3 WY778. Kollef MH. The role of selective digestive tract decontamination on mortality and respiratory tract infections. A meta-analysis. *Chest* 1994; **105**: 1101-8.
- 4 WY946. Liberati A, D'Amico R, Pifferi *et al.* Antibiotic prophylaxis to reduce respiratory tract infections and mortality in adults receiving intensive care. *The Cochrane Database of Systematic Reviews* 2004, Issue 1. Art. No.: CD000022. DOI: 10.1002/14651858.CD000022.pub2.
- 10 WY763. de Jonge E, Schultz MJ, Spanjaard L *et al.* Effects of selective decontamination of digestive tract on mortality and acquisition of resistant bacteria in intensive care: a randomised controlled trial. *Lancet* 2003; **362**: 1011-16.
- 12 WY775. Lingnau W, Berger J, Javorsky F *et al.* Changing bacterial ecology during a five-year period of selective intestinal decontamination. *J Hosp Infect* 1998; **39**: 195-206.

BSAC	Considered Judgement form HAP Treatment Working Party
Question 1 continued	
Is there any evidence that:	
d. Selective Digestive Tract Decontamination (SDD) is cost effective?	
Reviewers — Dr Robert Masterton and Dr Angela Galloway	
1. Volume of evidence:	
There is a body of evidence ^{11,13,14,15,16,17} from randomised controlled trials (RCT) structured to assess clinical outcome where four (two from Spain ^{13,15} one from France ¹⁴ and one from The Netherlands ¹⁷) investigated cost effectiveness in relation to cost per survivor.	
2. Applicability:	
Fully.	
3. Generalisability:	
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.	
4. Consistency:	
Highly consistent.	
5. Clinical impact:	
There is a significant clinical impact demonstrated for morbidity and mortality.	
6. Other factors:	
Pharmacy and other opportunity costs and resource implications need to be considered. In additional SDD programmes require concomitant antimicrobial resistance surveillance activity.	

7. Evidence statement:	Evidence grading
All four randomized controlled trials which assessed costs per survivor demonstrated that against this criterion, SDD is a cost effective procedure. ^{13,14,15,17}	1-
8. Recommendation:	
While initial costs to implement SDD may be higher than standard management, use of SDD can be cost effective in terms of individual cost per survivor. Costs vary between countries.	B
Some estimate of local cost should be made for SDD protocols in each unit.	GPP

References:	
11	WY769. Nardi G, Di Silvestre AD, De Monte A <i>et al.</i> Reduction in Gram-positive pneumonia and antibiotic consumption following the use of a SDD protocol including nasal and oral mupirocin. <i>Eur J Emerg Med</i> 2001; 8 : 203-14.

- 13 WY1450. Sanchez GM, Cambronero Galache JA, Lopez DJ *et al.* Effectiveness and cost of selective decontamination of the digestive tract in critically ill intubated patients. A randomized, double-blind, placebo-controlled, multicenter trial. *Am J Respir Crit Care Med* 1998; **158**: 908-16.
- 14 WY960. Korinek AM, Laisne MJ, Nicolas MH *et al.* Selective decontamination of the digestive tract in neurosurgical intensive care unit patients: a double-blind, randomized, placebo-controlled study. *Crit Care Med* 1993; **21**: 1466-73.
- 15 WY959. Rocha LA, Martin MJ, Pita S *et al.* Prevention of nosocomial infection in critically ill patients by selective decontamination of the digestive tract. A randomized, double blind, placebo-controlled study. *Intensive Care Med* 1992; **18**: 398-404.
- 16 WY776. Quinio B, Albanese J, Bues-Charbit M *et al.* Selective decontamination of the digestive tract in multiple trauma patients. A prospective double-blind, randomized, placebo-controlled study. *Chest* 1996; **109**: 765-72.
- 17 WY969. Stoutenbeek CP, van Saene HKF, Zandstra DF. Prevention of multiple organ system failure by selective decontamination of the digestive tract in multiple trauma patients. In: Faist E, Baue AE, Schildberg FW ed. *Immune Consequences of Trauma, Shock and Sepsis*. Lengerich: Pabst Science Publishers 1996; 1055-66.

BSAC	Considered Judgement form HAP Treatment Working Party	
Question 2 - Is there any evidence of benefit from the use of prophylactic parenteral antibiotics in:		
a. 'at-risk' patients?		
Reviewers — Dr Martin Street and Prof Alan Knox		
1. Volume of evidence:		
<p>There are three randomised controlled trials (RCTs) that assess the prophylactic use of parenteral antibiotics alone to reduce HAP.^{18,19,20} In the first of the RCTs described, Sirvent <i>et al.</i> compared the use of prophylactic cefuroxime (1500mg bd) to conventional practice (control) in 105 ventilated patients comatose due to trauma, stroke or surgery and observed a significant reduction in microbiologically confirmed pneumonia ($p=0.007$) from 50% in the control group to 24% in the treatment group.¹⁸ The dosage used however was a treatment dose.</p> <p>In the second RCT, Kimura and colleagues randomised 40 patients with severe burns requiring ventilator support to placebo or prophylactic treatment with trimethoprim-sulfamethoxazole (TMP-SMX). The incidence of methicillin-resistant <i>Staphylococcus aureus</i> (MRSA) pneumonia was reduced from 37% to 5% ($p=0.017$) with TMP-SMX. The later study showed trends for a reduction in mortality but the study was underpowered to demonstrate significance.¹⁹</p> <p>In this RCT, Acquarolo and colleagues randomised 38 comatose patients to either 3 days prophylaxis with ampicillin-sulbactam or conventional treatment (control). A reduced incidence of HAP was noticed in those receiving antibiotics (21% vs 57.9% $p=0.002$ in the control group). Unfortunately this study enrolled the least number of patients and the observers were not blinded to the treatment allocation.²⁰</p>		
2. Applicability:		
The data is applicable.		
3. Generalisability:		
The evidence is limited to burns and comatose patients.		
4. Consistency:		
The evidence is consistent across two RCTs.		
5. Clinical impact:		
Limited to burns and comatose patients.		
6. Other factors:		
None.		
7. Evidence statement:	Evidence grading	
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. No assessment of the potential for	1-	

resistance emergence was assessed in these studies.	
8. Recommendation:	
No recommendation for use of systemic antibiotic prophylaxis alone can be made but only as part of an SDD regimen.	B
The magnitude of treatment effect from systemic antibiotic prophylaxis alone is less than that from SDD and SDD is thus to be preferred.	GPP
Future Research Recommendation Further studies are required in these patients to assess the value of systemic antibiotic prophylaxis in patients at risk of HAP.	

References:	
18	WY828. Sirvent JM, Torres A, El-Ebiary M <i>et al.</i> Protective effect of intravenously administered cefuroxime against nosocomial pneumonia in patients with structural coma. <i>Am J Respir Crit Care Med</i> 1997; 155 : 1729-34.
19	WY827. Kimura A, Mochizuki T, Nishizawa K <i>et al.</i> Trimethoprim-sulfamethoxazole for the prevention of methicillin-resistant <i>Staphylococcus aureus</i> pneumonia in severely burned patients. <i>J Trauma</i> 1998; 45 : 383-7.
20	WY1611. Acquarolo A, Urli T, Perone G <i>et al.</i> Antibiotic prophylaxis of early onset pneumonia in critically ill comatose patients. A randomized study. <i>Intensive Care Med</i> 2005; 31 : 510-16.

BSAC	Considered Judgement form HAP Treatment Working Party	
Question 2 continued		
Is there any evidence of benefit from the use of prophylactic antibiotics in: b. perioperative surgical prophylaxis?		
Reviewers — Dr Martin Street and Prof Alan Knox		
1. Volume of evidence:		
There was one cohort study by Schilling <i>et al.</i> , which examined the effect of prophylactic antibiotic therapy during surgery but this study did not report information on pneumonia outcomes. ²¹		
2. Applicability:		
Not applicable.		
3. Generalisability:		
Not applicable.		
4. Consistency:		
Not applicable.		
5. Clinical impact:		
Not applicable.		
6. Other factors:		
Not applicable.		
7. Evidence statement:		Evidence grading
There is no evidence that supports or refutes the view that perioperative surgical prophylaxis will reduce the risk of pneumonia.		-
8. Recommendation:		
No recommendation can be made on use of prophylactic perioperative systemic antibiotics alone to prevent HAP.		-
Future Research Recommendation		
Further studies are required to assess if there is any value in the use of prophylactic perioperative systemic antibiotics to prevent HAP.		
References:		
21	WY622. Schilling J, Michalopoulos A, Geroulanos S. Antibiotic prophylaxis in gastroduodenal surgery. <i>Hepato-Gastroenterology</i> 1997; 44 : 116-20.	

BSAC	Considered Judgement form HAP Treatment Working Party
Question 6 - What are the optimal empirical and definitive antibiotic therapies of patients with HAP?	
Reviewers — Dr Martin Street, Dr Erwin Brown and Dr Robert Masterton	
1. Volume of evidence:	
<p>There is a large body of evidence from randomised controlled trials (RCTs) carried out over the past three decades. However, several of the earlier studies evaluated antibiotics which 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 recognised in most UK hospitals. Moreover, there are no well-conducted studies which have undertaken pharmacoeconomic or health economic evaluations.</p> <p>Few studies 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 of the available data is that the primary microbiological evaluations are invariably related to patients whose pathogens were susceptible to the trial antibiotics.</p> <p>Only six studies recruited 200 or more patients to both treatment and comparator arms.^{22,23,24,25,26,27}</p> <p>Only five studies were randomised double blind studies.^{22,23,27,28,29,30}</p> <p>In several studies so few patients were enrolled that the likelihood of a type II error is high.^{29,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57}</p> <p>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 hospitalisation. For all of these reasons it is not possible to identify the optimal antibiotic regimen.</p> <p>There are some data that demonstrate that the influence in Ventilator Associated Pneumonia (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.^{53,58,59,60,61,62,63}</p> <p>There are few studies that differentiate between Gram positive^{22,23,64,65} and Gram negative pathogens alone^{29,42,47,51,52,55,66,67}. Most studies looked at a mix of Gram positive and negative pathogens^{24,25,27,32,33,34,36,37,39,44,46,48,49,50,54,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88}.</p> <p>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 outcome.^{23,25,26,34,48,68,75,80}</p>	
2. Applicability:	
Generally applicable across all patients suffering from HAP.	

3. Generalisability:
Fully.
4. Consistency:
Whereas evidence is consistent this relates to studies powered to demonstrate equivalence rather than superiority.
5. Clinical impact:
Trials demonstrate the importance of administering appropriate antimicrobial treatment in terms of the incidences of morbidity, mortality and adverse events and cost.
6. Other factors:
None.

7. Evidence statement:	Evidence grading
Whereas the pathogens associated with late-onset HAP (and their susceptibility patterns) are highly variable (see HAP Diagnosis Considered Judgements Table 1 in <i>Question 3 – What organisms are isolated from respiratory specimens in patients with suspected HAP?</i>) those associated with early-onset infections are few in number and remarkably consistent from centre to centre.	2+
Analysis by organism: <i>Pseudomonas aeruginosa</i> Infection caused by <i>P.aeruginosa</i> is associated with a significantly higher incidence of treatment failure than those caused by other organisms. ^{27,79,80,}	1+
Sub-group analysis of studies in which imipenem was one of the antibiotics evaluated has shown statistically increased incidences of treatment failure compared with ceftazidime ($p=0.0004$) ^{39,77} or piperacillin/tazobactam ($p=0.004$). ⁷³	1+
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 <i>P.aeruginosa</i> , although, overall, the latter produced higher clinical and microbiological cure rates ($p =0.04$ and 0.006 respectively). ⁸¹	1+
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 <i>P.aeruginosa</i> 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 to 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 <i>P. aeruginosa</i> ²⁷	1+
Analysis by organism: MRSA The efficacies of two novel antibiotics have been evaluated as therapy of patients with infections caused specifically by Gram-positive bacteria, in	1+

particular MRSA: quinapristin/dalfopristin ⁶⁴ and linezolid ²³ versus vancomycin, and linezolid versus teicoplanin ³⁰ . It is unlikely that any of these studies had sufficient power to demonstrate superiority.	
There were two analyses of the combined data from two double blind studies. 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. ²² The second analysis in VAP patients showed increased survival (p=0.01), bacterial eradication (p=0.001) and clinical cure (p=0.001) rates. ⁸⁹ However, although more than 1000 patients were evaluated, only 160 of these actually had documented infection caused by MRSA.	1+
8. Recommendation:	
The choice of empirical antibiotic therapy of patients with HAP in an individual unit should be based on 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.	A
Treatment with an appropriate antibiotic should be started as soon as possible in order to reduce mortality.	A
No recommendation can be made regarding the optimal antibiotic regimen for patients with HAP suspected or proven to be caused by <i>P.aeruginosa</i> . Treatment options include ceftazidime, ciprofloxacin, meropenem and piperacillin/tazobactam	GPP
On the basis of the few published studies, we are unable to make a firm recommendation on the use of linezolid or a glycopeptide as optimal treatment of patients with HAP or VAP caused by MRSA.	GPP
For patients with early-onset infections (fewer than five 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.	GPP
For patients with early-onset infections (fewer than five 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.	GPP

References:

- | | |
|----|---|
| 22 | WY905. Wunderink RG, Rello J, Cammarata SK <i>et al</i> . Linezolid vs Vancomycin: Analysis of Two Double-Blind Studies of Patients with Methicillin-Resistant Staphylococcus aureus Nosocomial Pneumonia. <i>Chest</i> 2003; 124 : 1789-97. |
| 23 | WY800 dual code WY868. Rubinstein E, Cammarata S, Oliphant T <i>et al</i> . Linezolid Nosocomial Pneumonia Study Group. Linezolid (PNU-100766) versus vancomycin in the treatment of hospitalized patients with nosocomial pneumonia: a randomized, |

- double-blind, multicenter study. *Clin Infect Dis* 2001; **32**: 402-12.
- 24 WY907. Norrby SR, Petermann W, Willcox PA *et al*. A comparative study of levofloxacin and ceftriaxone in the treatment of hospitalized patients with pneumonia. *Scand J Infect Dis* 1998; **30**: 397-404.
- 25 WY909. Wolff M. Comparison of strategies using ceftazidime and ceftazidime for empiric treatment of pneumonia in intensive care patients. *Antimicrob Agents and Chemother* 1998; **42**: 28-36.
- 26 WY878. Rodloff AC, Laubenthal HJ, Bastian A *et al*. Comparative study of the cost-/effectiveness relationship of initial therapy with imipenem/cilastatin in nosocomial pneumonia. [German] *Anesthesiol Intensivmed Notfallmed Schmerzther* 1996; **31**: 172-80.
- 27 WY708. Fink MP, Snyderman DR, Niederman MS *et al*. Treatment of severe pneumonia in hospitalized patients: results of a multicenter, randomized, double-blind trial comparing intravenous ciprofloxacin with imipenem-cilastatin. *Antimicrob Agents and Chemother* 1994; **38**: 547-57.
- 28 WY863. Wunderink RG, Cammarata SK, Oliphant TH *et al*. Linezolid Nosocomial Pneumonia Study Group. Continuation of a randomized, double-blind, multicenter study of linezolid versus vancomycin in the treatment of patients with nosocomial pneumonia. *Clin Ther* 2003; **25**: 980-92.
- 29 WY844 dual code WY870. Le Conte G, Potel E, Clementi A *et al*. Administration of tobramycin aerosols in patients with nosocomial pneumonia: a preliminary study. *Presse Med* 2000; **29**: 76-8.
- 30 WY1614. Cepeda JA, Whitehouse T, Cooper B *et al*. Linezolid versus teicoplanin in the treatment of Gram-positive infections in the critically ill: a randomized, double-blind, multicentre study. *J Antimicrob Chemother* 2004; **53**: 345-55.
- 31 WY833. Georges B, Archambaud M, Saivin S *et al*. Continuous versus intermittent cefepime infusion in critical care patients. Preliminary findings. *Pathol Biol* 1999; **47**: 483-5.
- 32 WY687. Cone LA, Woodard DR, Stoltzman DS *et al*. Ceftazidime versus treatment of pneumonia and bacteremia. *Antimicrob Agents Chemother* 1985; **28**: 33-6.
- 33 WY888 dual code WY 824. Torres A, de Celis R, Rabinad E *et al*. Therapeutic efficacy of the combination of aztreonam with cefotaxime in the treatment of severe nosocomial pneumonia. Comparative study against amikacin combined with cefotaxime. *Chemotherapy* 1989; **35** Suppl 1: 15-24.
- 34 WY697. Rapp RP, Billeter M, Hatton J *et al*. Intravenous ciprofloxacin versus ceftazidime for treatment of nosocomial pneumonia and urinary tract infection. *Clin Pharm* 1991; **10**: 49-55.
- 35 WY872. Gao DW, Liu CL, Zhang JC. Observation of the therapeutic effect of cefepime in the treatment of nosocomial pneumonia. *Chin Pharm J* 1999; **34**: 624-6.
- 36 WY688. Rapp RP, Young B, Foster TS *et al*. Ceftazidime versus tobramycin/ticarcillin in treating hospital acquired pneumonia and bacteremia.

- Pharmacotherapy* 1984; **4**: 211-15.
- 37 WY867. Nicolau DP, McNabb J, Lacy MK *et al.* Continuous versus intermittent administration of ceftazidime in intensive care unit patients with nosocomial pneumonia. *Int J Antimicrob Agents* 2001; **17**: 497-504.
- 38 WY884. Heinrich R, Mitschka J. Multi-center, randomised comparative study of ceftazidime vs. cefotaxime in the treatment of patients 65 years of age and older with nosocomial bacterial pulmonary and urinary tract infections. *International Journal of Experimental & Clinical Chemotherapy* 1991; **4**: 40-7.
- 39 WY694. Hartenauer U, Weilemann LS, Bodmann KF *et al.* Comparative clinical trial of ceftazidime and imipenem/cilastatin in patients with severe nosocomial pneumonias and septicaemias. *J Hosp Infect* 1990; **15**: 61-4.
- 40 WY914. Trenholme GM, Schmitt BA, Spear J *et al.* Randomized study of intravenous/oral ciprofloxacin versus ceftazidime in the treatment of hospital and nursing home patients with lower respiratory tract infections. *Am J Med* 1989; **87** Suppl: S116-8.
- 41 WY831. Siami GA, Wilkins WT, Bess DT *et al.* Comparison of ciprofloxacin with imipenem in the treatment of severe pneumonia in hospitalised geriatric patients. *Drugs* 1995; **49**: 436-8.
- 42 WY700. Schentag JJ, Vari AJ, Winslade NE *et al.* Treatment with aztreonam or tobramycin in critical care patients with nosocomial gram-negative pneumonia. *Am J Med* 1985; **78**: 34-41.
- 43 WY2022. Villavicencio J, Asensio de Fernandez ME, Ramirez CA *et al.* Intravenous ciprofloxacin or ceftazidime in selected infections. A prospective, randomized, controlled study. *Am J Med* 1989; **87** Suppl: 191S-4S.
- 44 WY880. Fekete T, Castellano M, Ramirez J *et al.* A randomised comparative trial of aztreonam plus cefazolin versus ceftazidime for the treatment of nosocomial pneumonia. *Drug Invest* 1994; **7**: 117-26.
- 45 WY695. Bassetti D, Cruciani M, Solbiati M *et al.* Comparative efficacy of ceftriaxone versus ceftazidime in the treatment of nosocomial lower respiratory tract infections. *Chemotherapy* 1991; **37**: 371-5.
- 46 WY711. Giamarellou H, Mandragos K, Bechrakis P *et al.* Pefloxacin versus imipenem in the therapy of nosocomial lung infections of intensive care unit patients. *J Antimicrob Chemother* 1990; **26**: 117-27.
- 47 WY918. Nolen TM, Phillips HL, Hall HJ *et al.* Comparison of aztreonam and tobramycin in the treatment of lower respiratory tract infections caused by gram-negative bacilli. *Rev Infect Dis* 1985; **7** Suppl: S666-8.
- 48 WY815 dual code WY881. Thomas PD, Daly S, Misan G *et al.* Comparison of the efficacy and adverse effect profile of cefotaxime, 3 g day⁻¹, and ceftriaxone, 2 g day⁻¹, in the treatment of nosocomial lower respiratory tract infections in ICU patients. *Eur Respir Rev* 1994; **4**: 321-8.
- 49 WY702. Mouton YJ, Beuscart C. Empirical monotherapy with meropenem in serious bacterial infections. *J Antimicrob Chemother* 1995; **36**: 145-56.

- 50 WY911. Bjornson HS, Ramirez-Ronda C, Saavedra S *et al.* Comparison of empiric aztreonam and aminoglycoside regimens in the treatment of serious gram-negative lower respiratory infections. *Clin Ther* 1993; **15**: 65-78.
- 51 WY802 dual code WY812. Beaucaire G. Evaluation of the efficacy and safety of isepamicin compared with amikacin in the treatment of nosocomial pneumonia and septicemia *J Chemother* 1995; **7** Suppl 2: 165-173
- 52 WY699. Rodriguez JR, Ramirez-Ronda CH, Nevarez M. Efficacy and safety of aztreonam versus tobramycin for aerobic gram-negative bacilli lower respiratory tract infections. *Am J Med* 1985; **78**: 42-3.
- 53 WY735. Singh N, Rogers P, Atwood CW *et al.* Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit. A proposed solution for indiscriminate antibiotic prescription. *Am J Respir Crit Care Med* 2000; **162**: 505-511.
- 54 WY685. Mandell LA, Nicolle LE, Ronald AR *et al.* A multicentre prospective randomized trial comparing ceftazidime with cefazolin/tobramycin in the treatment of hospitalized patients with non-pneumococcal pneumonia. *J Antimicrob Chemother* 1983; **12**: 9-20.
- 55 WY850. Kljucar S. Ceftazidime with and without tobramycin versus azlocillin plus tobramycin in the therapy of bronchopulmonary infections in intensive care patients. *Infection* 1987; **15** Suppl: S185-91.
- 56 WY1520. Warren JW, Miller EH Jr, Fitzpatrick B *et al.* A randomized, controlled trial of cefoperazone vs. cefamandole-tobramycin in the treatment of putative, severe infections with Gram-negative bacilli. *Rev Infect Dis* 1983; **5** Suppl: S173-80.
- 57 WY1521 Brown RB, Lemeshow S, Teres D. Moxalactam vs carbenicillin plus tobramycin: Treatment of nosocomial Gram-negative bacillary pneumonias in non-neutropenic patients. *Current Therapeutic Research* 1984; **36**: 557-64.
- 58 WY1601. Luna CM, Vujacich P, Niederman MS *et al.* Impact of BAL Data on the Therapy and Outcome of Ventilator-Associated Pneumonia. *Chest* 1997; **111**: 676-85.
- 59 WY1602. Trouillet JL, Chastre J, Vuagnat A *et al.* Ventilator-associated Pneumonia Caused by Potentially Drug-resistant Bacteria. *Am J Respir Crit Care Med* 1998; **157**: 531-9.
- 60 WY1603. Iregui M, Ward S, Sherman G *et al.* Clinical Importance of Delays in the Initiation of Appropriate Antibiotic Treatment for Ventilator-Associated Pneumonia. *Chest* 2002; **122**: 262-8.
- 61 WY1604. Kollef MH, Ward S. The Influence of Mini-BAL Cultures on Patient Outcomes Implications for the Antibiotic Management of Ventilator-Associated Pneumonia. *Chest* 1998; **113**: 412-20.
- 62 WY2023. Alvarez-Lerma F. Modification of empiric antibiotic treatment in patients with pneumonia acquired in the intensive care unit. ICU-Acquired Pneumonia Study Group. *Intensive Care Med.* 1996; **22**: 387-94.

- 63 WY1605. Dupont H, Mentec H, Sollet JP *et al.* Impact of appropriateness of initial antibiotic therapy on the outcome of ventilator-associated pneumonia. *Intensive Care Med* 200; **27**:355-62.
- 64 WY795 dual code WY869. Fagon J, Patrick H, Haas DW *et al.* Treatment of Gram-positive nosocomial pneumonia: Prospective randomized comparison of quinupristin/dalfopristin versus vancomycin. *Am J Respir Crit Care Med* 2000; **161**: 753-62.
- 65 WY863. Wunderink RG, Cammarata SK, Oliphant TH *et al.* Continuation of a randomized, double-blind, multicenter study of linezolid versus vancomycin in the treatment of patients with nosocomial pneumonia. *Clin Ther* 2003; **25**: 980-92.
- 66 WY887. Rivera-Vazquez CR, Ramirez-Ronda CH, Rodriguez JR *et al.* A comparative analysis of aztreonam + clindamycin versus tobramycin + clindamycin or amikacin + mezlocillin in the treatment of gram-negative lower respiratory tract infections. *Chemotherapy* 1989; **35** Suppl 1: 89-100.
- 67 WY707. Giamarellou H, Perdikaris G, Galanakis N *et al.* Pefloxacin versus ceftazidime in the treatment of a variety of gram-negative-bacterial infections. *Antimicrob Agents Chemother* 1989; **33**: 1362-7.
- 68 WY871. Beaucaire G, Nicolas MH, Martin C *et al.* Comparative study of combined cefepime-amikacin versus ceftazidime combined with amikacin in the treatment of nosocomial pneumonias in ventilated patients. Multicenter group study. *Ann Fr Anesth Reanim* 1999; **18**: 186-95.
- 69 WY864. Zanetti G, Bally F, Greub G *et al.* Cefepime versus Imipenem-Cilastatin for Treatment of Nosocomial Pneumonia in Intensive Care Unit Patients: A Multicenter, Evaluator-Blind, Prospective, Randomized Study. *Antimicrob Agents and Chemother* 2003; **47**: 3442-7.
- 70 WY865. Alvarez-Lerma F, Insausti-Ordenana J, Jorda- G *et al.* Efficacy and tolerability of piperacillin/tazobactam versus ceftazidime in association with amikacin for treating nosocomial pneumonia in intensive care patients: a prospective randomized multicenter trial. *Intensive Care Med* 2001; **27**: 493-502.
- 71 WY873. Hopkins DW, Daniel R. Trovafloxacin vs ciprofloxacin +/- clindamycin/metronidazole in patients with nosocomial pneumonia. *Drugs* 1999; **58**: 323-5.
- 72 WY874. Brun-Buisson C, Sollet JP, Schweich H *et al.* Treatment of ventilator-associated pneumonia with piperacillin-tazobactam/amikacin versus ceftazidime/amikacin: a multicenter, randomized controlled trial. VAP Study Group. *Clin Infect Dis* 1998; **26**: 346-54.
- 73 WY906. Jaccard C, Troillet N, Harbarth S *et al.* Prospective randomized comparison of imipenem-cilastatin and piperacillin-tazobactam in nosocomial pneumonia or peritonitis. *Antimicrob Agents and Chemother* 1998; **42**: 2966-72.
- 74 WY908. Willis R, Gaines J, Nelson M *et al.* Cefepime vs cefotaxime in the treatment of pneumonia. *Infect Med* 1998; **15**: 636-43.
- 75 WY834. Saginur R, Garber G, Darling G, *et al.* Prospective, randomized comparison

- of intravenous and oral ciprofloxacin. *Can J Infect Dis* 1997; **8**: 89-94.
- 76 WY879. Shah PM, Stille W. Cefotaxime versus ceftriaxone for the treatment of nosocomial pneumonia: Results of a multicenter study. *Diagn Microbiol Infect Dis* 1995; **22**: 171-2.
- 77 WY816 dual code WY882. Norrby SR, Finch RG, Glauser M. Monotherapy in serious hospital-acquired infections: A clinical trial of ceftazidime versus imipenem/cilastatin. *J Antimicrob Chemother* 1993; **31**: 927-37.
- 78 WY886. Beuscart C, Leroy O, Mouton Y *et al.* Prospective randomized controlled study of the ceftazidim-pefloxacin combination versus the ceftazidim-amikacin combination in the empirical treatment of pneumonia and nosocomial septicemia in intensive care units. *Path Biol* 1989; **37**: 496-9.
- 79 WY709. Cometta A, Baumgartner JD, Lew D *et al.* Prospective randomized comparison of imipenem monotherapy with imipenem plus netilmicin for treatment of severe infections in nonneutropenic patients. *Antimicrob Agents Chemother* 1994; **38**: 1309-13.
- 80 WY862. West M, Boulanger BR, Fogarty C *et al.* Levofloxacin compared with imipenem/cilastatin followed by ciprofloxacin in adult patients with nosocomial pneumonia: a multicenter, prospective, randomized, open-label study. *Clin Ther* 2003; **25**: 485-506.
- 81 WY1519. Sieger B, Berman SJ, Geckler RW *et al.* Empiric treatment of hospital-acquired lower respiratory tract infections with meropenem or ceftazidime with tobramycin: a randomized study. Meropenem Lower Respiratory Infection Group. *Crit Care Med* 1997; **25**: 1663-70.
- 82 WY849. Koehler CO and Arnold H. Controlled clinical study of ceftazidime (3 x 1 g daily) versus piperacillin + tobramycin in patients with nosocomial pneumonia. *International Journal of Experimental & Clinical Chemotherapy* 1990; **3**: 211-8.
- 83 WY843. Alvarez LF. Efficacy of monotherapy by meropenem in ventilator-associated pneumonia. *J Chemother* 2001; **13**: 70-81.
- 84 WY686. Mandell LA, Nicolle LE, Ronald AR *et al.* A prospective randomized trial of ceftazidime versus cefazolin/tobramycin in the treatment of hospitalized patients with pneumonia. *J Antimicrob Chemother* 1987; **20**: 95-107.
- 85 WY691. Rubinstein E, Lode H, Grassi C. Ceftazidime monotherapy vs. ceftriaxone/tobramycin for serious hospital-acquired Gram-negative infections. Antibiotic Study Group. *Clin Infect Dis* 1995; **20**: 1217-28.
- 86 WY693. Mangi RJ, Greco T, Ryan J *et al.* Cefoperazone versus combination antibiotic therapy of hospital-acquired pneumonia. *Am J Med* 1988; **84**: 68-74.
- 87 WY692. Mangi RJ, Ryan J, Berenson C *et al.* Cefoperazone versus ceftazidime monotherapy of nosocomial pneumonia. *Am J Med* 1988; **85**: 44-8.
- 88 WY710. Joshi M, Bernstein J, Solomkin J *et al.* Piperacillin/tazobactam plus tobramycin versus ceftazidime plus tobramycin for the treatment of patients with nosocomial lower respiratory tract infection. Piperacillin/tazobactam Nosocomial

Pneumonia Study Group. *J Antimicrob Chemother* 1994; **43**: 389-97.

- 89 WY1624. Kollef MH, Rello J, Cammarata SK *et al*. Clinical cure and survival in Gram-positive ventilator-associated pneumonia: retrospective analysis of two double-blind studies comparing linezolid with vancomycin. *Intensive Care Med* 2004; **30**: 388-94.

BSAC	Considered Judgement form HAP Treatment Working Party
Question 7 - Is there any evidence that antibiotic treatment protocols for HAP are effective or cost effective?	
Reviewers — Prof Dilip Nathwani and Prof Mark Wilcox	
1. Volume of evidence:	
<p>There is one randomised controlled trial (RCT) in patients with VAP on a medical ICU. The active antibiotic discontinuation policy resulted in a 2 day reduction of antibiotic use with associated cost savings without altering patient outcome or hospital stay.⁹⁰</p> <p>Most of the literature is community acquired pneumonia (CAP) focused or looks at prevention or diagnosis rather than treatment of HAP. The literature relating to the impact of guidelines or protocols has been more extensively evaluated and reviewed in two key articles.^{91,92} These reviews conclude that guidelines or 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 hypothesise 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 to studies by Ibrahim <i>et al.</i>⁹³ and Singh <i>et al.</i>⁵³</p> <p>The Ibrahim study is an uncontrolled before and after study examining the impact of ventilator associated pneumonia (VAP) guidelines on the primary outcome of appropriateness of initial empirical antibiotic therapy judged against a subsequent positive culture. Secondary outcomes included duration of therapy, mortality, secondary episode of VAP and length of stay. The study was imbalanced by significant differences in baseline prevalence of co-morbidities such as Chronic Obstructive Pulmonary Disease (COPD), Congestive Cardiac Failure (CCF) and serum albumin and 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%, $p>0.001$), reduction in duration of antibiotics (14.8 –8.6 days $p>0.001$) and the second episode 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 support the intervention of a VAP guideline on any of the outcomes defined.⁹³</p> <p>Singh <i>et al.</i>⁵³ is a non blinded RCT utilising a modified Clinical Pulmonary Infection Score (CPIS) of six or less to select patients at low risk of HAP who would be deemed suitable for early discontinuation (three days) of empirical therapy for HAP. It compares a standard duration and choice of therapy which is at the clinician's discretion with ciprofloxacin monotherapy. The results confirm that early discontinuation of empirical therapy is not associated with increased mortality, has a shorter duration of stay and cost, and a lower antibiotic resistance or incidence of superinfection. It also indicates that a protocol for empirical therapy that guides clinical decision making related to duration of therapy based on the CPIS, can 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 minimise antibiotic polypharmacy and the duration in the comparator</p>	

(standard therapy) arm as the study progressed. The study requires validation in different populations and in more severe forms of HAP.

2. Applicability:

Modest

3. Generalisability:

Limited

4. Consistency:

Limited

5. Clinical impact:

Modest

6. Other factors:

Extrapolating evidence of a better quality from a closely related disease, is useful to evaluate effectiveness of guidelines in HAP/VAP

7. Evidence statement:

Evidence from two studies were considered: one uncontrolled study⁹³ suggests that antibiotic treatment protocols improve the appropriateness and duration of HAP treatment.

A non blinded RCT⁵³ suggests that a protocol for empirical therapy for patients at low risk of HAP can reduce the duration of unnecessary antibiotic therapy, reduce length of stay and cost, reduce the incidence of superinfection and resistance without compromising effectiveness.⁵³

Evidence grading

1-

8. Recommendation:

Guidelines or protocols for empirical therapy of HAP/VAP may be able to improve economic and microbiological outcomes without compromising efficacy in certain clinical settings. Data from intervention studies in VAP appear to support this broad principle.

C

Future Research Recommendation

The impact of specific HAP/VAP guidelines or protocols on heterogeneous populations and in severe HAP/VAP requires further evaluation through well designed, prospective, intervention studies.

References:

- 53 WY735. Singh N, Rogers P, Atwood CW *et al*. Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit. A proposed solution for indiscriminate antibiotic prescription. *Am J Respir Crit Care Med* 2000; **162**: 505-511.
- 90 WY1627. Micek ST, Ward S, Fraser VJ, Kollef MH. A randomized controlled trial of an antibiotic discontinuation policy for clinically suspected ventilator-associated pneumonia. *Chest* 2004; **125**: 1791-99.
- 91 WY2021. Barlow G. Pneumonia guidelines in practice. In: Gould I and van der Meer

- JW, ed. *Antibiotic Policies: Theory and practice*. New York: Kluwer Academic/Plenum Publishers, 2005; 37-61.
- 92 WY1609. Barlow G, Lamping D, Davey P *et al*. Evaluating Outcomes in Community Acquired Pneumonia: A Guide for patients, Physicians and Policy Makers. *Lancet Infect Dis* 2003; **3**: 476-88.
- 93 WY949. Ibrahim EH, Ward S, Sherman G *et al*. Experience with a clinical guideline for the treatment of ventilator-associated pneumonia. *Crit Care Med* 2001; **29**: 1109-15.

BSAC	Considered Judgement form HAP Treatment Working Party
Question 9 – Is there evidence to suggest that the pharmacodynamic and pharmacokinetic profiles of different antibiotics are important in selecting therapy/regimens or in influencing outcome?	
Reviewers — Dr Robert Masterton/Dr Martin Street	
1. Volume of evidence:	
There was a small volume of evidence from three cohort studies. ^{94,95,96}	
2. Applicability:	
The studies are applicable to assessing pharmacokinetic (PK), pharmacodynamic (PD) and other surrogate markers in guiding treatment for HAP.	
3. Generalisability:	
However the studies are retrospective theoretical modelling rather than prospective randomised trials therefore it is not reasonable or appropriate to extrapolate the findings to treatment of HAP as a whole.	
4. Consistency:	
The evidence is consistent but the volume of evidence is small – composed largely of work from one group undertaking research in this field (three cohort studies). ^{94,95,96}	
5. Clinical impact:	
The available data suggest that PK/PD approaches may have significant clinical impact in the treatment of HAP but prospective randomised controlled trials are required to explore this potential.	
6. Other factors:	
None.	

7. Evidence statement:	Evidence grading
There are insufficient clinical data to recommend evaluation of PK and PD features as a guide to treatment selection in HAP.	2-
8. Recommendation:	
PK and PD modelling should not at this time be used to guide treatment selections in HAP.	D
Further Research Recommendation	
Prospective randomised controlled trials should be progressed to explore the value of PK and PD in guiding treatment choice in HAP.	

References:

- 94 WY1546. Forrest A, Nix DE, Ballou CH *et al.* Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients. *Antimicrob Agents Chemother* 1993; **37**: 1073-81.
- 95 WY1547. Thomas JK, Forrest A, Bhavnani SM *et al.* Pharmacodynamic evaluation of factors associated with the development of bacterial resistance in acutely ill patients during therapy. *Antimicrob Agents Chemother* 1998; **42**: 521-7.
- 96 WY1545. Kashuba AD, Nafziger AN, Drusano GL *et al.* Optimizing aminoglycoside therapy for nosocomial pneumonia caused by Gram-negative bacteria. *Antimicrob Agents Chemother* 1999; **43**: 623-9.

BSAC	Considered Judgement form HAP Treatment Working Party
Question 10 – Is there evidence of differing outcomes based on whether monotherapy or combination therapy is used and does this depend upon selected antibiotic classes?	
Reviewers — Dr Erwin Brown and Prof Mark Wilcox	
1. Volume of evidence:	
<p>There are no systematic reviews which are directly relevant to this question. Sixteen randomised controlled trials (RCTs) 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, ticarcillin) with an aminoglycoside).^{32,35,49,54,55,56,57,79,81,82,83,84,85,86,97,98} Of these, only two compared the same beta-lactam with and without an aminoglycoside. The study carried out by Cometta <i>et al.</i> compared imipenem with the combination of imipenem and netilmicin and demonstrated no statistically significant difference in terms of clinical outcome.⁷⁹ Kljucar <i>et al.</i> compared ceftazidime with ceftrazidime and tobramycin, but also included a third arm comprising the combination of azlocillin and tobramycin.⁵⁵ Again, no statistically significant differences in terms of outcomes were reported, although patient numbers were too small to allow any meaningful conclusions to be drawn.⁵⁵ Of the 14 remaining studies nine detected no statistically significant differences in clinical outcomes.^{32,35,49,54,57,85,84,86,98} Three studies demonstrated a significant benefit favouring monotherapy (meropenem <i>versus</i> ceftazidime plus tobramycin,^{81,83} cefotaxime <i>versus</i> various combination regimens⁹⁷). However, the investigators' conclusions are questionable. The study performed by Alvarez <i>et al.</i> is underpowered,⁸³ in the study of Sieger <i>et al.</i> patients received sub-therapeutic dosages of aminoglycosides⁸¹ and in that of Fendandez-Guerro <i>et al.</i> the comparator regimen was not standardised.⁹⁷ Only five of the studies employed appropriate methodologies and adequate statistical power to detect significant differences between treatment groups; in all five cases monotherapy and combination therapy were shown to be equivalent.^{49,54,79,84,85}</p> <p>The study undertaken by Kljucar <i>et al.</i> was the only RCT in which different combination regimens were compared, but, as stated above, only small numbers of patients were enrolled, thereby precluding any reliable conclusions.⁵⁵</p>	
2. Applicability:	
The five studies are applicable and appropriately powered. ^{49,54,79,84,85}	
3. Generalisability:	
Only two of the above mentioned five studies were specific to patients with HAP. ^{54,84}	
4. Consistency:	
The findings are consistent.	
5. Clinical impact:	
See Recommendations.	
6. Other factors:	
For toxicity see Evidence Summary.	

7. Evidence statement:	Evidence grading
There is no evidence that clinical or bacteriological response rates can be improved with combination therapy (cephalosporins, carbapenems or penicillins and an aminoglycoside).	1+
There is no evidence that one class of beta-lactams (cephalosporins, carbapenems or penicillins) is more effective than the others, in terms of clinical or bacteriological response rates, when used in combination with an aminoglycoside.	1-
<p>The evidence demonstrates equivalence of monotherapy and combination therapy. However, few studies were sufficiently powered to enable superiority to be detected.</p> <p>Equivalence of monotherapy and combination therapy is supported by the systematic review by Paul <i>et al.</i> in the treatment of non-neutropenic patients with serious infections.⁹⁹ However, increased incidences of toxicity were observed in patients receiving combination therapy that included an aminoglycoside.</p>	1+
8. Recommendation:	
Monotherapy is equivalent to combination therapy in patients with HAP.	A
Adding an aminoglycoside confers no therapeutic benefit.	GPP
When considering combination therapy recognition needs to be given to potential direct and indirect consequences including adverse events and costs.	GPP
Future Research Recommendation	
Further studies designed to compare the efficacies of different beta-lactam classes, when used in combinations with aminoglycosides, are required.	B

References:	
32	WY687. Cone LA, Woodard DR, Stoltzman DS <i>et al.</i> Ceftazidime versus treatment of pneumonia and bacteremia. <i>Antimicrob Agents Chemother</i> 1985; 28 : 33-6.
35	WY688. Rapp RP, Young B, Foster TS <i>et al.</i> Ceftazidime versus tobramycin/ticarcillin in treating hospital acquired pneumonia and bacteremia. <i>Pharmacotherapy</i> 1984; 4 : 211-15.
49	WY702. Mouton YJ, Beuscart C. Empirical monotherapy with meropenem in serious bacterial infections. <i>J Antimicrob Chemother</i> 1995; 36 : 145-56.
54	WY685. Mandell LA, Nicolle LE, Ronald AR <i>et al.</i> A multicentre prospective randomized trial comparing ceftazidime with cefazolin/tobramycin in the treatment of hospitalized patients with non-pneumococcal pneumonia. <i>J Antimicrob Chemother</i> 1983; 12 : 9-20.
55	WY850. Kljucar S. Ceftazidime with and without tobramycin versus azlocillin plus

- tobramycin in the therapy of bronchopulmonary infections in intensive care patients. *Infection* 1987; **15** Suppl: S185-91.
- 56 WY1520. Warren JW, Miller EH Jr, Fitzpatrick B *et al*. A randomized, controlled trial of cefoperazone vs. cefamandole-tobramycin in the treatment of putative, severe infections with Gram-negative bacilli. *Rev Infect Dis* 1983; **5** Suppl: S173-80.
- 57 WY1521. Brown RB, Lemeshow S, Teres D. Moxalactam vs carbenicillin plus tobramycin: Treatment of nosocomial Gram-negative bacillary pneumonias in non-neutropenic patients. *Current Therapeutic Research* 1984; **36**: 557-64.
- 79 WY709. Cometta A, Baumgartner JD, Lew D *et al*. Prospective randomized comparison of imipenem monotherapy with imipenem plus netilmicin for treatment of severe infections in nonneutropenic patients. *Antimicrob Agents Chemother* 1994; **38**: 1309-13.
- 81 WY1519. Sieger B, Berman SJ, Geckler RW *et al*. Empiric treatment of hospital-acquired lower respiratory tract infections with meropenem or ceftazidime with tobramycin: a randomized study. Meropenem Lower Respiratory Infection Group. *Crit Care Med* 1997; **25**: 1663-70.
- 82 WY849. Koehler CO and Arnold H. Controlled clinical study of ceftazidime (3 x 1 g daily) versus piperacillin + tobramycin in patients with nosocomial pneumonia. *International Journal of Experimental & Clinical Chemotherapy* 1990; **3**: 211-8.
- 83 WY843. Alvarez LF. Efficacy of monotherapy by meropenem in ventilator-associated pneumonia. *J Chemother* 2001; **13**: 70-81.
- 84 WY686. Mandell LA, Nicolle LE, Ronald AR *et al*. A prospective randomized trial of ceftazidime versus cefazolin/tobramycin in the treatment of hospitalized patients with pneumonia. *J Antimicrob Chemother* 1987; **20**: 95-107.
- 85 WY691. Rubinstein E, Lode H, Grassi C. Ceftazidime monotherapy vs. ceftriaxone/tobramycin for serious hospital-acquired Gram-negative infections. Antibiotic Study Group. *Clin Infect Dis* 1995; **20**: 1217-28.
- 86 WY693. Mangi RJ, Greco T, Ryan J *et al*. Cefoperazone versus combination antibiotic therapy of hospital-acquired pneumonia. *Am J Med* 1988; **84**: 68-74.
- 97 WY1522. Fernandez-Guerrero M, Gudiol F, Rodriguez-Torres A *et al*. Nosocomial pneumonia: comparative multicentre trial between monotherapy with cefotaxime and treatment with antibiotic combinations. *Infection* 1991; **19** Suppl: S320-5.
- 98 WY845. Speich R, Imhof E, Vogt M *et al*. Efficacy, safety, and tolerance of piperacillin/tazobactam compared to co-amoxiclav plus an aminoglycoside in the treatment of severe pneumonia. *Eur J Clin Microbiol Infect Dis* 1998; **17**: 313-7.
- 99 WY1516. Paul M, Benuri-Silbiger I, Soares-Weiser K *et al*. B lactam monotherapy versus B lactam-aminoglycoside combination therapy for sepsis in immunocompetent patients: systematic review and meta-analysis of randomised trials. *BMJ* 2004; **328**: 668.

BSAC	Considered Judgement form HAP Treatment Working Party
Question 11 - Are data available to support the efficacy of instilled or nebulised therapy as an adjunct to standard therapy?	
Reviewers — Dr Erwin Brown and Prof Dilip Nathwani	
1. Volume of evidence:	
<p>Five papers provide information about patients with ventilator associated pneumonia (VAP). Of these, three, a randomised controlled trial (RCT),¹⁰⁰ an uncontrolled before and after study,¹⁰¹ and a case – control study,¹⁰² contain data relating to pharmacokinetics, in particular the concentrations of drugs in distal bronchial secretions or sputum, but not in specimens obtained by bronchoalveolar lavage (BAL). Only two RCTs^{29,103} assess the efficacy of topical therapy in terms of clinical outcome and tolerability in patients with VAP. One compared tobramycin with placebo, both instilled via the endotracheal (ET) tube, in patients who also received parenteral regimens comprising tobramycin and either ceftazolin or piperacillin.¹⁰³ The other RCT also compared tobramycin with placebo, although, in this case, both were nebulised via ET tubes; the patients also received parenteral antibiotics (beta-lactams plus tobramycin).²⁹</p> <p>Although there is insufficient evidence that the administration of topical therapy has an effect on clinical or bacteriological outcomes in patients with VAP, there is one systematic review involving patients with cystic fibrosis who were treated with aerosolised anti-pseudomonal antibiotics that concluded that this intervention improved lung function and reduced the frequency of acute exacerbations in this patient population.¹⁰⁴</p>	
2. Applicability:	
<p>All of the pharmacokinetic studies demonstrate that high concentrations of aminoglycosides are achieved in bronchial secretions irrespective of whether they are instilled or nebulised/aerosolised via an endotracheal (ET) tube. In contrast, ceftazidime¹⁰² and imipenem¹⁰⁰ achieved significantly higher concentrations when administered by instillation than by nebulisation. Instillation appears to be the preferred route of administration.</p> <p>In the one study in which outcome was assessed¹⁰³ only 45 of the 85 patients recruited were evaluable. The pathogens were predominantly coliforms. There is insufficient evidence to allow conclusions to be reached about the efficacy of this intervention in patients with infections caused by Gram-positive bacteria, including meticillin-resistant <i>Staphylococcus aureus</i> (MRSA).</p>	
3. Generalisability:	
<p>The failure to measure drug concentrations in the alveoli, lung parenchyma and epithelial lining fluid (ELF) is a deficiency that applies to all the pharmacokinetic studies.</p> <p>Information regarding clinical outcomes is limited, thereby precluding generalisations in this patient population.</p>	
4. Consistency:	
<p>Based on the available pharmacokinetic data, endotracheal instillation is the preferred route of administration owing to the higher concentrations of ceftazidime and imipenem achievable</p>	

in bronchial secretions, ease of administration and tolerability.

As only one RCT evaluated clinical outcome¹⁰³ it is not possible to reach a conclusion regarding consistency.

5. Clinical impact:

There are insufficient data to allow accurate conclusions to be reached regarding the effect of topical therapy on clinical outcome.

6. Other factors:

Instillation of tobramycin (and presumably other aminoglycosides as well) may result in marked accumulation of the drug in the sera of patients with renal failure, with the attendant potential for the development of toxicity. Supraventricular tachycardia has also been observed in patients who have received tobramycin instilled endotracheally.

7. Evidence statement:	Evidence grading
<p>Pharmacokinetic studies^{100,101,102} have demonstrated that high concentrations of aminoglycosides are achieved in bronchial secretions when these drugs are administered by either instillation or nebulisation via an ET tube. However, ceftazidime¹⁰² and imipenem¹⁰⁰ achieved significantly higher concentrations when administered by instillation than by nebulisation. Instillation therefore appears to be the preferred route of administration, based on the higher local concentrations achieved with some drugs, ease of administration and tolerability.</p>	3
<p>One RCT¹⁰³ evaluated the efficacy of an antibiotic (tobramycin) instilled via ET tubes in patients with VAP caused by Gram-negative bacteria who also received parenteral therapy. Compared with a placebo (instilled via an ET tube), 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 and the emergence of resistance in the culture-positive population was not observed more frequently in the study group 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 nebulised 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.²⁹ These limitations, together with the absence of other robust evidence, precludes any firm conclusions regarding the efficacy of topical antibiotics as adjunctive therapy in patients with VAP.²⁹</p>	1-
8. Recommendation:	
<p>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 cannot be recommended.</p>	-

If antibiotics are to be given endotracheally, then instillation through an ET tube, as opposed to nebulisation, is the preferred route of administration.	D
<p>Further research recommendation</p> <p>A systematic review of patients with cystic fibrosis has demonstrated that aerosolised anti-pseudomonal antibiotics are associated with a statistically significant reduction in the incidences of acute exacerbations.¹⁰⁴ The applicability of these findings to patients with VAP is uncertain, but is worthy of further study.</p>	-

References:

- 29 WY844 dual code WY870. Le Conte G, Potel E, Clementi A *et al.* Administration of tobramycin aerosols in patients with nosocomial pneumonia: a preliminary study. *Presse Med* 2000; **29**: 76-8.
- 100 WY1534. Badia JR, Soy D, Adrover M *et al.* Disposition of instilled versus nebulized tobramycin and imipenem in ventilated intensive care unit (ICU) patients. *J Antimicrob Chemother* 2004; **54**: 508-14.
- 101 WY1526. Palmer LB, Smaldone GC, Simon SR *et al.* Aerosolized antibiotics in mechanically ventilated patients: delivery and response. *Crit Care Med* 1998; **26**: 31-9.
- 102 WY1529. Bressolle F, de la Coussaye JE, Ayoub R *et al.* Endotracheal and aerosol administrations of ceftazidime in patients with nosocomial pneumonia: pharmacokinetics and absolute bioavailability. *Antimicrob Agents Chemother* 1992; **36**: 1404-11.
- 103 WY1531. Brown RB, Kruse JA, Counts GW *et al.* Double-blind study of endotracheal tobramycin in the treatment of Gram-negative bacterial pneumonia. The Endotracheal Tobramycin Study Group. *Antimicrob Agents Chemother* 1990; **34**: 269-72.
- 104 WY921. Ryan G, Mukhopadhyay S, Singh M. Nebulised anti-pseudomonal antibiotics for cystic fibrosis. *The Cochrane Database of Systematic Reviews* 2003, Issue 3. Art. No.: CD001021. DOI: 10.1002/14651858.CD001021.

BSAC	Considered Judgement form HAP Treatment Working Party
Question 12 – Are there clear criteria available for the initiation of step down therapy e.g. intravenous to oral?	
Reviewers — Dr Martin Street and Prof Mark Wilcox	
1. Volume of evidence:	
<p>There are three randomised controlled trials (RCTs)^{75,105,106} that assess the efficacy of switching from intravenous to oral therapy. All studies were designed to examine the comparators antibiotics rather than to specifically address the benefits of switching from intravenous to oral formulations.</p> <p>The three RCTs all had low numbers of patients and were not powered to show differences between treatment only comparisons.</p> <p>The study reports did not include definitive information on the criteria that were used to determine when it was acceptable to switch patients from intravenous to oral formulations.</p>	
2. Applicability:	
Not applicable.	
3. Generalisability:	
Poor.	
4. Consistency:	
Poor.	
5. Clinical impact:	
None.	
6. Other factors:	
None.	

7. Evidence statement:	Evidence grading
The available evidence is uninterpretable from the point of view of answering this question.	2-
8. Recommendation:	
No recommendation.	-
Future Research Recommendation	
Further research is required.	

References:

- 75 WY834. Saginur R, Garber G, Darling G, *et al.* Prospective, randomized comparison of intravenous and oral ciprofloxacin. *Can J Infect Dis* 1997; **8**: 89-94.
- 105 WY832. Bassaris HP, Williams HD, Daniel R. IV– to–Oral switch therapy with Trovafloxacin compared with IV. *Drugs* 1999; **58**: 309-11.
- 106 WY835. Solbrig A, Bucher I, Sieber W *et al.* Comparative study on the clinical efficacy and compatibility of fleroxacin versus ciprofloxacin. *Atemwegs-und Lungenkrkh* 1996; **22** Suppl: S615-9.

BSAC	Considered Judgement form HAP Treatment Working Party	
<p>Question 15 - What other treatment modalities are important in the management of HAP?</p> <p>a. Activated Protein C</p>		
Reviewers — Dr Martin Street and Prof Alan Knox		
<p>1. Volume of evidence:</p>		
<p>There is one large, good quality randomised controlled trial (RCT) trial conducted in hospitalised patients with sepsis and organ failure comparing activated protein C to placebo. The RCT included 164 centres recruiting patients of which more than 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 ($p=0.005$).¹⁰⁷</p>		
<p>2. Applicability:</p>		
Applicable to HAP patients with multi organ failure.		
<p>3. Generalisability:</p>		
Limited to HAP patients with multi organ failure.		
<p>4. Consistency:</p>		
Not applicable – only one study available.		
<p>5. Clinical impact:</p>		
Important for HAP patients with multi organ failure.		
<p>6. Other factors:</p>		
None		
<p>7. Evidence statement:</p>		<p>Evidence grading</p>
<p>There is one large, good quality RCT trial conducted in hospitalised patients with sepsis and organ failure comparing activated protein C to placebo.¹⁰⁷ No breakdown of hospital or community acquired pneumonia was provided therefore this trial cannot be considered as definitive proof of improvement in pneumonia 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.</p>		<p>1-</p>
<p>8. Recommendation:</p>		
<p>Patients with sepsis, organ failure and hospital-acquired pneumonia should be considered for treatment with activated protein C according to the manufacturer's guidance for use.</p>		<p>B</p>

Future Research Recommendation

Further studies with activated protein C in patients with diagnosed hospital acquired pneumonia are required.

References:

107 WY1517. Bernard GR, Vincent JL, Laterre PF *et al.* Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001; **344**: 699-709.

BSAC	Considered Judgement form HAP Treatment Working Party	
Question 15 continued		
What other treatment modalities are important in the management of HAP?		
b. Granulocyte-Colony Stimulating Factor (G-CSF)		
Reviewers — Dr Martin Street and Prof Alan Knox		
1. Volume of evidence:		
There is one systematic review ¹⁰⁸ and four randomised controlled trials (RCTs) studies identified that examined HAP outcomes. ^{109,110,111,112} One study by Wunderink and colleagues assessed safety only ¹⁰⁹ and the studies by Meyanci <i>et al.</i> and Hartmann <i>et al.</i> could not be used to draw conclusions as the patient numbers were small. ^{110,112} The study by Root, the third of the RCTs, assessed efficacy in 701 patients with acquired or nosocomial pneumonia (no breakdown provided) randomised to treatment with G-CSF or placebo, in addition to antibiotic therapy. ¹¹¹ The study demonstrated no improvement in pneumonia outcomes in terms of mortality with G-CSF compared to placebo. ¹¹¹		
2. Applicability:		
The evidence is applicable.		
3. Generalisability:		
The evidence is generalisable to HAP.		
4. Consistency:		
The evidence is consistent.		
5. Clinical impact:		
G-CSF is not beneficial.		
6. Other factors:		
None.		
7. Evidence statement:	Evidence grading	
The evidence suggests that G-CSF is not beneficial in the treatment of HAP.	1+	
8. Recommendation:		
Patients with sepsis and pneumonia should not be treated with G-CSF.	A	
References:		
108	WY1615. Cheng AC, Stephens DP, Currie BJ. Granulocyte-colony stimulating factor (G-CSF) as an adjunct to antibiotics in the treatment of pneumonia in adults (Review). <i>Cochrane Database of Systematic Reviews</i> 2004; CD004400.	
109	WY956. Wunderink RG, Leeper KV, Schein R <i>et al.</i> Filgrastim in patients with pneumonia and severe sepsis or septic shock. <i>Chest</i> 2001; 119 : 523-29.	

- 110 WY955. Meyanci G, Oz H. Combination of granulocyte colony-stimulating factor and antibacterial drugs for the treatment of ventilatory associated nosocomial pneumonia. *Middle East J Anesthesiol* 2001; **16**: 91-101.
- 111 WY954. Root RK, Lodato RF, Patrick W *et al*. Multicenter, double-blind, placebo-controlled study of the use of filgrastim in patients hospitalized with pneumonia and severe sepsis. *Crit Care Med* 2003; **31**: 367-73.
- 112 WY1009. Hartmann P, Lammertink J, Mansmann G *et al*. A randomized, placebo-controlled study of the use of filgrastim in non neutropenic patients with nosocomial pneumonia. *Eur J Med Res* 2005; **10**: 29-35.

BSAC	Considered Judgement form HAP Treatment Working Party	
Question 15 continued What other treatment modalities are important in the management of HAP? c. physiotherapy		
Reviewers — Dr Martin Street and Prof Alan Knox		
1. Volume of evidence:		
There is one randomised controlled trial (RCT) trial, by Graham and Bradley, which assessed the effect of physiotherapy, in combination with positive-pressure breathing on pneumonia outcomes. This study evaluated 54 patients with clinically diagnosed pneumonia for efficacy. No significant difference in outcomes (duration of fever, length of stay and mortality) was observed. No breakdown of acquired or nosocomial pneumonia was provided and no assessment of the power of the study to detect a difference was undertaken. ¹¹³		
2. Applicability:		
There is only one RCT which does not distinguish between the different pneumonias (HAP versus VAP).		
3. Generalisability:		
Limited to one study.		
4. Consistency:		
Limited to one study.		
5. Clinical impact:		
Limited to one study.		
6. Other factors:		
None.		
7. Evidence statement:	Evidence grading	
There is no evidence to support improved pneumonia outcomes with chest physiotherapy.	1-	
8. Recommendation:		
Chest physiotherapy is not recommended for the direct management of patients with HAP due to lack of evidence demonstrating improved outcomes.	B	
References:		
113 WY631. Graham WG, Bradley DA. Efficacy of chest physiotherapy and intermittent positive-pressure breathing in the resolution of pneumonia. <i>N Engl J Med</i> 1978; 299 : 624-7.		

BSAC	Considered Judgement form HAP Treatment Working Party	
Question 15 continued		
What other treatment modalities are important in the management of HAP? d. steroids		
Reviewers — Dr Martin Street and Prof Alan Knox		
1. Volume of evidence:		
Evidence assessing the effect steroids on HAP was very limited. Two cohort studies were identified. ^{114,115} One of these studies was a pilot study performed by Mouton <i>et al.</i> ¹¹⁴ and the other was Patterson and colleague's work which was based on an out break of <i>Branhamella catarrhalis</i> . ¹¹⁵ Neither of these studies was deemed relevant to the question.		
2. Applicability:		
The evidence is limited.		
3. Generalisability:		
The evidence is limited.		
4. Consistency:		
The evidence is limited.		
5. Clinical impact:		
None.		
6. Other factors:		
None.		
7. Evidence statement:		Evidence grading
There is an absence of evidence to support the use of steroids as a treatment modality for HAP.		-
8. Recommendation:		
No recommendation can be made on use of steroid therapy to treat HAP.		-
References:		
114	WY652. Monton C, Ewig S, Torres A <i>et al.</i> Role of glucocorticoids on inflammatory response in nonimmunosuppressed patients with pneumonia: a pilot study. <i>Eur Respir J</i> 1999; 14 : 218-20.	
115	WY644. Patterson TF, Patterson JE, Masecar BL <i>et al.</i> A nosocomial outbreak of <i>Branhamella catarrhalis</i> confirmed by restriction endonuclease analysis. <i>J Infect Dis</i> 1988; 157 : 996-1001.	

References

- 1 WY784. Nathens AB, Marshall JC. Selective decontamination of the digestive tract in surgical patients: a systematic review of the evidence. *Arch Surg* 1999; **134**: 170-6.
- 2 WY627. D'Amico R, Pifferi S, Leonetti C *et al*. Effectiveness of antibiotic prophylaxis in critically ill adult patients: systematic review of randomised controlled trials. *BMJ* 1998; **316**: 1275-85.
- 3 WY778. Kollef MH. The role of selective digestive tract decontamination on mortality and respiratory tract infections. A meta-analysis. *Chest* 1994; **105**: 1101-8.
- 4 WY946. Liberati A, D'Amico R, Pifferi *et al*. Antibiotic prophylaxis to reduce respiratory tract infections and mortality in adults receiving intensive care. *The Cochrane Database of Systematic Reviews* 2004, Issue 1. Art. No.: CD000022. DOI: 10.1002/14651858.CD000022.pub2.
- 5 WY942. Heyland DK, Cook DJ, Jaeschke R, *et al*. Selective decontamination of the digestive tract. An overview. *Chest* 1994; **105**: 1221-9.
- 6 WY941. Selective Decontamination of the Digestive Tract Trialists' Collaborative Group. Meta-analysis of randomised controlled trials of selective decontamination of the digestive tract. *BMJ* 1993; **307**: 525-32.
- 7 WY772. van Nieuwenhoven CA, Buskens E, van Tiel FH *et al*. Relationship between methodological trial quality and the effects of selective digestive decontamination on pneumonia and mortality in critically ill patients. *JAMA* 2001; **286**: 335-40.
- 8 WY1600. Krueger WA, Lenhart FP, Neeser G *et al*. Influence of combined intravenous and topical antibiotic prophylaxis on the incidence of infections, organ dysfunctions and mortality in critically ill surgical patients: A prospective, stratified, randomised, double-blind, placebo-controlled clinical trial. *Am J Respir Crit Care Med* 2002; **166**: 1029-37.
- 9 WY764. Filos KS. Selective decontamination of the digestive tract: Implications for the critically ill patient. A critical review. *Archives of Hellenic Medicine* 2003; **20** Suppl A: 78-86.
- 10 WY763. de Jonge E, Schultz MJ, Spanjaard L *et al*. Effects of selective decontamination of digestive tract on mortality and acquisition of resistant bacteria in intensive care: a randomised controlled trial. *Lancet* 2003; **362**: 1011-16.
- 11 WY769. Nardi G, Di Silvestre AD, De Monte A *et al*. Reduction in Gram-positive pneumonia and antibiotic consumption following the use of a SDD protocol including nasal and oral mupirocin. *Eur J Emerg Med* 2001; **8**: 203-14.
- 12 WY775. Lingnau W, Berger J, Javorsky F *et al*. Changing bacterial ecology during a five-year period of selective intestinal decontamination. *J Hosp Infect* 1998; **39**: 195-206.
- 13 WY1450. Sanchez GM, Cambronero Galache JA, Lopez DJ *et al*. Effectiveness and cost of selective decontamination of the digestive tract in critically ill intubated

-
- patients. A randomized, double-blind, placebo-controlled, multicenter trial. *Am J Respir Crit Care Med* 1998; **158**: 908-16.
- 14 WY960. Korinek AM, Laisne MJ, Nicolas MH *et al*. Selective decontamination of the digestive tract in neurosurgical intensive care unit patients: a double-blind, randomized, placebo-controlled study. *Crit Care Med* 1993; **21**: 1466-73.
- 15 WY959. Rocha LA, Martin MJ, Pita S *et al*. Prevention of nosocomial infection in critically ill patients by selective decontamination of the digestive tract. A randomized, double blind, placebo-controlled study. *Intensive Care Med* 1992; **18**: 398-404.
- 16 WY776. Quinio B, Albanese J, Bues-Charbit M *et al*. Selective decontamination of the digestive tract in multiple trauma patients. A prospective double-blind, randomized, placebo-controlled study. *Chest* 1996; **109**: 765-72.
- 17 WY969. Stoutenbeek CP, van Saene HKF, Zandstra DF. Prevention of multiple organ system failure by selective decontamination of the digestive tract in multiple trauma patients. In: Faist E, Baue AE, Schildberg FW ed. *Immune Consequences of Trauma, Shock and Sepsis*. Lengerich: Pabst Science Publishers 1996; 1055-66.
- 18 WY828. Sirvent JM, Torres A, El-Ebiary M *et al*. Protective effect of intravenously administered cefuroxime against nosocomial pneumonia in patients with structural coma. *Am J Respir Crit Care Med* 1997; **155**: 1729-34.
- 19 WY827. Kimura A, Mochizuki T, Nishizawa K *et al*. Trimethoprim-sulfamethoxazole for the prevention of methicillin-resistant *Staphylococcus aureus* pneumonia in severely burned patients. *J Trauma* 1998; **45**: 383-7.
- 20 WY1611. Acquarolo A, Urli T, Perone G *et al*. Antibiotic prophylaxis of early onset pneumonia in critically ill comatose patients. A randomized study. *Intensive Care Med* 2005; **31**: 510-16.
- 21 WY622. Schilling J, Michalopoulos A, Geroulanos S. Antibiotic prophylaxis in gastroduodenal surgery. *Hepato-Gastroenterology* 1997; **44**: 116-20.
- 22 WY905. Wunderink RG, Rello J, Cammarata SK *et al*. Linezolid vs Vancomycin: Analysis of Two Double-Blind Studies of Patients with Methicillin-Resistant *Staphylococcus aureus* Nosocomial Pneumonia. *Chest* 2003; **124**: 1789-97.
- 23 WY800 dual code WY868. Rubinstein E, Cammarata S, Oliphant T *et al*. Linezolid Nosocomial Pneumonia Study Group. Linezolid (PNU-100766) versus vancomycin in the treatment of hospitalized patients with nosocomial pneumonia: a randomized, double-blind, multicenter study. *Clin Infect Dis* 2001; **32**: 402-12.
- 24 WY907. Norrby SR, Petermann W, Willcox PA *et al*. A comparative study of levofloxacin and ceftriaxone in the treatment of hospitalized patients with pneumonia. *Scand J Infect Dis* 1998; **30**: 397-404.
- 25 WY909. Wolff M. Comparison of strategies using cefpirome and ceftazidime for empiric treatment of pneumonia in intensive care patients. *Antimicrob Agents and Chemother* 1998; **42**: 28-36.
- 26 WY878. Rodloff AC, Laubenthal HJ, Bastian A *et al*. Comparative study of the cost-/effectiveness relationship of initial therapy with imipenem/cilastatin in nosocomial

-
- pneumonia. [German] *Anesthesiol Intensivmed Notfallmed Schmerzther* 1996; **31**: 172-80.
- 27 WY708. Fink MP, Snyderman DR, Niederman MS *et al.* Treatment of severe pneumonia in hospitalized patients: results of a multicenter, randomized, double-blind trial comparing intravenous ciprofloxacin with imipenem-cilastatin. *Antimicrob Agents and Chemother* 1994; **38**: 547-57.
- 28 WY863. Wunderink RG, Cammarata SK, Oliphant TH *et al.* Linezolid Nosocomial Pneumonia Study Group. Continuation of a randomized, double-blind, multicenter study of linezolid versus vancomycin in the treatment of patients with nosocomial pneumonia. *Clin Ther* 2003; **25**: 980-92.
- 29 WY844 dual code WY870. Le Conte G, Potel E, Clementi A *et al.* Administration of tobramycin aerosols in patients with nosocomial pneumonia: a preliminary study. *Presse Med* 2000; **29**: 76-8.
- 30 WY1614. Cepeda JA, Whitehouse T, Cooper B *et al.* Linezolid versus teicoplanin in the treatment of Gram-positive infections in the critically ill: a randomized, double-blind, multicentre study. *J Antimicrob Chemother* 2004; **53**: 345-55.
- 31 WY833. Georges B, Archambaud M, Saivin S *et al.* Continuous versus intermittent cefepime infusion in critical care patients. Preliminary findings. *Pathol Biol* 1999; **47**: 483-5.
- 32 WY687. Cone LA, Woodard DR, Stoltzman DS *et al.* Ceftazidime versus treatment of pneumonia and bacteremia. *Antimicrob Agents Chemother* 1985; **28**: 33-6.
- 33 WY888 dual code WY 824. Torres A, de Celis R, Rabinad E *et al.* Therapeutic efficacy of the combination of aztreonam with cefotaxime in the treatment of severe nosocomial pneumonia. Comparative study against amikacin combined with cefotaxime. *Chemotherapy* 1989; **35** Suppl 1: 15-24.
- 34 WY697. Rapp RP, Billeter M, Hatton J *et al.* Intravenous ciprofloxacin versus ceftazidime for treatment of nosocomial pneumonia and urinary tract infection. *Clin Pharm* 1991; **10**: 49-55.
- 35 WY872. Gao DW, Liu CL, Zhang JC. Observation of the therapeutic effect of cefepime in the treatment of nosocomial pneumonia. *Chin Pharm J* 1999; **34**: 624-6.
- 36 WY688. Rapp RP, Young B, Foster TS *et al.* Ceftazidime versus tobramycin/ticarcillin in treating hospital acquired pneumonia and bacteremia. *Pharmacotherapy* 1984; **4**: 211-15.
- 37 WY867. Nicolau DP, McNabb J, Lacy MK *et al.* Continuous versus intermittent administration of ceftazidime in intensive care unit patients with nosocomial pneumonia. *Int J Antimicrob Agents* 2001; **17**: 497-504.
- 38 WY884. Heinrich R, Mitschka J. Multi-center, randomised comparative study of ceftazidime vs. cefotaxime in the treatment of patients 65 years of age and older with nosocomial bacterial pulmonary and urinary tract infections. *International Journal of Experimental & Clinical Chemotherapy* 1991; **4**: 40-7.

-
- 39 WY694. Hartenauer U, Weilemann LS, Bodmann KF *et al.* Comparative clinical trial of ceftazidime and imipenem/cilastatin in patients with severe nosocomial pneumonias and septicaemias. *J Hosp Infect* 1990; **15**: 61-4.
- 40 WY914. Trenholme GM, Schmitt BA, Spear J *et al.* Randomized study of intravenous/oral ciprofloxacin versus ceftazidime in the treatment of hospital and nursing home patients with lower respiratory tract infections. *Am J Med* 1989; **87** Suppl: S116-8.
- 41 WY831. Siami GA, Wilkins WT, Bess DT *et al.* Comparison of ciprofloxacin with imipenem in the treatment of severe pneumonia in hospitalised geriatric patients. *Drugs* 1995; **49**: 436-8.
- 42 WY700. Schentag JJ, Vari AJ, Winslade NE *et al.* Treatment with aztreonam or tobramycin in critical care patients with nosocomial gram-negative pneumonia. *Am J Med* 1985; **78**: 34-41.
- 43 WY2022. Villavicencio J, Asensio de Fernandez ME, Ramirez CA *et al.* Intravenous ciprofloxacin or ceftazidime in selected infections. A prospective, randomized, controlled study. *Am J Med* 1989; **87** Suppl: 191S-4S.
- 44 WY880. Fekete T, Castellano M, Ramirez J *et al.* A randomised comparative trial of aztreonam plus cefazolin versus ceftazidime for the treatment of nosocomial pneumonia. *Drug Invest* 1994; **7**: 117-26.
- 45 WY695. Bassetti D, Cruciani M, Solbiati M *et al.* Comparative efficacy of ceftriaxone versus ceftazidime in the treatment of nosocomial lower respiratory tract infections. *Chemotherapy* 1991; **37**: 371-5.
- 46 WY711. Giamarellou H, Mandragos K, Bechrakis P *et al.* Pefloxacin versus imipenem in the therapy of nosocomial lung infections of intensive care unit patients. *J Antimicrob Chemother* 1990; **26**: 117-27.
- 47 WY918. Nolen TM, Phillips HL, Hall HJ *et al.* Comparison of aztreonam and tobramycin in the treatment of lower respiratory tract infections caused by gram-negative bacilli. *Rev Infect Dis* 1985; **7** Suppl: S666-8.
- 48 WY815 dual code WY881. Thomas PD, Daly S, Misan G *et al.* Comparison of the efficacy and adverse effect profile of cefotaxime, 3 g day⁻¹, and ceftriaxone, 2 g day⁻¹, in the treatment of nosocomial lower respiratory tract infections in ICU patients. *Eur Respir Rev* 1994; **4**: 321-8.
- 49 WY702. Mouton YJ, Beuscart C. Empirical monotherapy with meropenem in serious bacterial infections. *J Antimicrob Chemother* 1995; **36**: 145-56.
- 50 WY911. Bjornson HS, Ramirez-Ronda C, Saavedra S *et al.* Comparison of empiric aztreonam and aminoglycoside regimens in the treatment of serious gram-negative lower respiratory infections. *Clin Ther* 1993; **15**: 65-78.
- 51 WY802 dual code WY812. Beaucaire G. Evaluation of the efficacy and safety of isepamicin compared with amikacin in the treatment of nosocomial pneumonia and septicaemia *J Chemother* 1995; **7** Suppl 2: 165 173

-
- 52 WY699. Rodriguez JR, Ramirez-Ronda CH, Nevarez M. Efficacy and safety of aztreonam versus tobramycin for aerobic gram-negative bacilli lower respiratory tract infections. *Am J Med* 1985; **78**: 42-3.
- 53 WY735. Singh N, Rogers P, Atwood CW *et al*. Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit. A proposed solution for indiscriminate antibiotic prescription. *Am J Respir Crit Care Med* 2000; **162**: 505-511.
- 54 WY685. Mandell LA, Nicolle LE, Ronald AR *et al*. A multicentre prospective randomized trial comparing ceftazidime with cefazolin/tobramycin in the treatment of hospitalized patients with non-pneumococcal pneumonia. *J Antimicrob Chemother* 1983; **12**: 9-20.
- 55 WY850. Kljucar S. Ceftazidime with and without tobramycin versus azlocillin plus tobramycin in the therapy of bronchopulmonary infections in intensive care patients. *Infection* 1987; **15** Suppl: S185-91.
- 56 WY1520. Warren JW, Miller EH Jr, Fitzpatrick B *et al*. A randomized, controlled trial of cefoperazone vs. cefamandole-tobramycin in the treatment of putative, severe infections with Gram-negative bacilli. *Rev Infect Dis* 1983; **5** Suppl: S173-80.
- 57 WY1521. Brown RB, Lemeshow S, Teres D. Moxalactam vs carbenicillin plus tobramycin: Treatment of nosocomial Gram-negative bacillary pneumonias in non-neutropenic patients. *Current Therapeutic Research* 1984; **36**: 557-64.
- 58 WY1601. Luna CM, Vujacich P, Niederman MS *et al*. Impact of BAL Data on the Therapy and Outcome of Ventilator-Associated Pneumonia. *Chest* 1997; **111**: 676-85.
- 59 WY1602. Trouillet JL, Chastre J, Vuagnat A *et al*. Ventilator-associated Pneumonia Caused by Potentially Drug-resistant Bacteria. *Am J Respir Crit Care Med* 1998; **157**: 531-9.
- 60 WY1603. Iregui M, Ward S, Sherman G *et al*. Clinical Importance of Delays in the Initiation of Appropriate Antibiotic Treatment for Ventilator-Associated Pneumonia. *Chest* 2002; **122**: 262-8.
- 61 WY1604. Kollef MH, Ward S. The Influence of Mini-BAL Cultures on Patient Outcomes Implications for the Antibiotic Management of Ventilator-Associated Pneumonia. *Chest* 1998; **113**: 412-20.
- 62 WY2023. Alvarez-Lerma F. Modification of empiric antibiotic treatment in patients with pneumonia acquired in the intensive care unit. ICU-Acquired Pneumonia Study Group. *Intensive Care Med*. 1996; **22**: 387-94.
- 63 WY1605. Dupont H, Mentec H, Sollet JP *et al*. Impact of appropriateness of initial antibiotic therapy on the outcome of ventilator-associated pneumonia. *Intensive Care Med* 2001; **27**:355-62.
- 64 WY795. dual code WY869. Fagon J, Patrick H, Haas DW *et al*. Treatment of Gram-positive nosocomial pneumonia: Prospective randomized comparison of quinupristin/dalfopristin versus vancomycin. *Am J Respir Crit Care Med* 2000; **161**: 753-62.

-
- 65 WY863. Wunderink RG, Cammarata SK, Oliphant TH *et al.* Continuation of a randomized, double-blind, multicenter study of linezolid versus vancomycin in the treatment of patients with nosocomial pneumonia. *Clin Ther* 2003; **25**: 980-92.
- 66 WY887. Rivera-Vazquez CR, Ramirez-Ronda CH, Rodriguez JR *et al.* A comparative analysis of aztreonam + clindamycin versus tobramycin + clindamycin or amikacin + mezlocillin in the treatment of gram-negative lower respiratory tract infections. *Chemotherapy* 1989; **35** Suppl 1: 89-100.
- 67 WY707. Giamarellou H, Perdikaris G, Galanakis N *et al.* Pefloxacin versus ceftazidime in the treatment of a variety of gram-negative-bacterial infections. *Antimicrob Agents Chemother* 1989; **33**: 1362-7.
- 68 WY871. Beaucaire G, Nicolas MH, Martin C *et al.* Comparative study of combined cefepime-amikacin versus ceftazidime combined with amikacin in the treatment of nosocomial pneumonias in ventilated patients. Multicenter group study. *Ann Fr Anesth Reanim* 1999; **18**: 186-95.
- 69 WY864. Zanetti G, Bally F, Greub G *et al.* Cefepime versus Imipenem-Cilastatin for Treatment of Nosocomial Pneumonia in Intensive Care Unit Patients: A Multicenter, Evaluator-Blind, Prospective, Randomized Study. *Antimicrob Agents and Chemother* 2003; **47**: 3442-7.
- 70 WY865. Alvarez-Lerma F, Insausti-Ordenana J, Jorda- G *et al.* Efficacy and tolerability of piperacillin/tazobactam versus ceftazidime in association with amikacin for treating nosocomial pneumonia in intensive care patients: a prospective randomized multicenter trial. *Intensive Care Med* 2001; **27**: 493-502.
- 71 WY873. Hopkins DW, Daniel R. Trovafloxacin vs ciprofloxacin +/- clindamycin/metronidazole in patients with nosocomial pneumonia. *Drugs* 1999; **58**: 323-5.
- 72 WY874. Brun-Buisson C, Sollet JP, Schweich H *et al.* Treatment of ventilator-associated pneumonia with piperacillin-tazobactam/amikacin versus ceftazidime/amikacin: a multicenter, randomized controlled trial. VAP Study Group. *Clin Infect Dis* 1998; **26**: 346-54.
- 73 WY906. Jaccard C, Troillet N, Harbarth S *et al.* Prospective randomized comparison of imipenem-cilastatin and piperacillin-tazobactam in nosocomial pneumonia or peritonitis. *Antimicrob Agents and Chemother* 1998; **42**: 2966-72.
- 74 WY908. Willis R, Gaines J, Nelson M *et al.* Cefepime vs cefotaxime in the treatment of pneumonia. *Infect Med* 1998; **15**: 636-43.
- 75 WY834. Saginur R, Garber G, Darling G, *et al.* Prospective, randomized comparison of intravenous and oral ciprofloxacin. *Can J Infect Dis* 1997; **8**: 89-94.
- 76 WY879. Shah PM, Stille W. Cefotaxime versus ceftriaxone for the treatment of nosocomial pneumonia: Results of a multicenter study. *Diagn Microbiol Infect Dis* 1995; **22**: 171-2.

-
- 77 WY816 dual code WY882. Norrby SR, Finch RG, Glauser M. Monotherapy in serious hospital-acquired infections: A clinical trial of ceftazidime versus imipenem/cilastatin. *J Antimicrob Chemother* 1993; **31**: 927-37.
- 78 WY886. Beuscart C, Leroy O, Mouton Y *et al.* Prospective randomized controlled study of the ceftazidim-pefloxacin combination versus the ceftazidim-amikacin combination in the empirical treatment of pneumonia and nosocomial septicemia in intensive care units. *Path Biol* 1989; **37**: 496-9.
- 79 WY709. Cometta A, Baumgartner JD, Lew D *et al.* Prospective randomized comparison of imipenem monotherapy with imipenem plus netilmicin for treatment of severe infections in nonneutropenic patients. *Antimicrob Agents Chemother* 1994; **38**: 1309-13.
- 80 WY862. West M, Boulanger BR, Fogarty C *et al.* Levofloxacin compared with imipenem/cilastatin followed by ciprofloxacin in adult patients with nosocomial pneumonia: a multicenter, prospective, randomized, open-label study. *Clin Ther* 2003; **25**: 485-506.
- 81 WY1519. Sieger B, Berman SJ, Geckler RW *et al.* Empiric treatment of hospital-acquired lower respiratory tract infections with meropenem or ceftazidime with tobramycin: a randomized study. Meropenem Lower Respiratory Infection Group. *Crit Care Med* 1997; **25**: 1663-70.
- 82 WY849. Koehler CO and Arnold H. Controlled clinical study of ceftazidime (3 x 1 g daily) versus piperacillin + tobramycin in patients with nosocomial pneumonia. *International Journal of Experimental & Clinical Chemotherapy* 1990; **3**: 211-8.
- 83 WY843. Alvarez LF. Efficacy of monotherapy by meropenem in ventilator-associated pneumonia. *J Chemother* 2001; **13**: 70-81.
- 84 WY686. Mandell LA, Nicolle LE, Ronald AR *et al.* A prospective randomized trial of ceftazidime versus cefazolin/tobramycin in the treatment of hospitalized patients with pneumonia. *J Antimicrob Chemother* 1987; **20**: 95-107.
- 85 WY691. Rubinstein E, Lode H, Grassi C. Ceftazidime monotherapy vs. ceftriaxone/tobramycin for serious hospital-acquired Gram-negative infections. Antibiotic Study Group. *Clin Infect Dis* 1995; **20**: 1217-28.
- 86 WY693. Mangi RJ, Greco T, Ryan J *et al.* Cefoperazone versus combination antibiotic therapy of hospital-acquired pneumonia. *Am J Med* 1988; **84**: 68-74.
- 87 WY692. Mangi RJ, Ryan J, Berenson C *et al.* Cefoperazone versus ceftazidime monotherapy of nosocomial pneumonia. *Am J Med* 1988; **85**: 44-8.
- 88 WY710. Joshi M, Bernstein J, Solomkin J *et al.* Piperacillin/tazobactam plus tobramycin versus ceftazidime plus tobramycin for the treatment of patients with nosocomial lower respiratory tract infection. Piperacillin/tazobactam Nosocomial Pneumonia Study Group. *J Antimicrob Chemother* 1994; **43**: 389-97.
- 89 WY1624. Kollef MH, Rello J, Cammarata SK *et al.* Clinical cure and survival in Gram-positive ventilator-associated pneumonia: retrospective analysis of two double-blind studies comparing linezolid with vancomycin. *Intensive Care Med* 2004; **30**: 388-94.

-
- 90 WY1627. Micek ST, Ward S, Fraser VJ, Kollef MH. A randomized controlled trial of an antibiotic discontinuation policy for clinically suspected ventilator-associated pneumonia. *Chest* 2004; **125**: 1791-99.
- 91 WY2021. Barlow G. Pneumonia guidelines in practice. In: Gould I and van der Meer JW, ed. *Antibiotic Policies: Theory and practice*. New York: Kluwer Academic/Plenum Publishers, 2005; 37-61.
- 92 WY1609. Barlow G, Lamping D, Davey P *et al*. Evaluating Outcomes in Community Acquired Pneumonia: A Guide for patients, Physicians and Policy Makers. *Lancet Infect Dis* 2003; **3**: 476-88.
- 93 WY949. Ibrahim EH, Ward S, Sherman G *et al*. Experience with a clinical guideline for the treatment of ventilator-associated pneumonia. *Crit Care Med* 2001; **29**: 1109-15.
- 94 WY1546. Forrest A, Nix DE, Ballow CH *et al*. Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients. *Antimicrob Agents Chemother* 1993; **37**: 1073-81.
- 95 WY1547. Thomas JK, Forrest A, Bhavnani SM *et al*. Pharmacodynamic evaluation of factors associated with the development of bacterial resistance in acutely ill patients during therapy. *Antimicrob Agents Chemother* 1998; **42**: 521-7.
- 96 WY1545. Kashuba AD, Nafziger AN, Drusano GL *et al*. Optimizing aminoglycoside therapy for nosocomial pneumonia caused by Gram-negative bacteria. *Antimicrob Agents Chemother* 1999; **43**: 623-9.
- 97 WY1522. Fernandez-Guerrero M, Gudiol F, Rodriguez-Torres A *et al*. Nosocomial pneumonia: comparative multicentre trial between monotherapy with cefotaxime and treatment with antibiotic combinations. *Infection* 1991;**19** Suppl: S320-5.
- 98 WY845. Speich R, Imhof E, Vogt M *et al*. Efficacy, safety, and tolerance of piperacillin/tazobactam compared to co-amoxiclav plus an aminoglycoside in the treatment of severe pneumonia. *Eur J Clin Microbiol Infect Dis* 1998; **17**: 313-7.
- 99 WY1516. Paul M, Benuri-Silbiger I, Soares-Weiser K *et al*. B lactam monotherapy versus B lactam-aminoglycoside combination therapy for sepsis in immunocompetent patients: systematic review and meta-analysis of randomised trials. *BMJ* 2004; **328**: 668.
- 100 WY1534. Badia JR, Soy D, Adrover M *et al*. Disposition of instilled versus nebulized tobramycin and imipenem in ventilated intensive care unit (ICU) patients. *J Antimicrob Chemother* 2004; **54**: 508-14.
- 101 WY1526. Palmer LB, Smaldone GC, Simon SR *et al*. Aerosolized antibiotics in mechanically ventilated patients: delivery and response. *Crit Care Med* 1998; **26**: 31-9.
- 102 WY1529. Bressolle F, de la Coussaye JE, Ayoub R *et al*. Endotracheal and aerosol administrations of ceftazidime in patients with nosocomial pneumonia: pharmacokinetics and absolute bioavailability. *Antimicrob Agents Chemother* 1992; **36**: 1404-11.

-
- 103 WY1531. Brown RB, Kruse JA, Counts GW *et al.* Double-blind study of endotracheal tobramycin in the treatment of Gram-negative bacterial pneumonia. The Endotracheal Tobramycin Study Group. *Antimicrob Agents Chemother* 1990; **34**: 269-72.
- 104 WY921. Ryan G, Mukhopadhyay S, Singh M. Nebulised anti-pseudomonal antibiotics for cystic fibrosis. *The Cochrane Database of Systematic Reviews* 2003, Issue 3. Art. No.: CD001021. DOI: 10.1002/14651858.CD001021.
- 105 WY832. Bassaris HP, Williams HD, Daniel R. IV- to-Oral switch therapy with Trovafloxacin compared with IV. *Drugs* 1999; **58**: 309-11.
- 106 WY835. Solbrig A, Bucher I, Sieber W *et al.* Comparative study on the clinical efficacy and compatibility of fleroxacin versus ciprofloxacin. *Atemwegs-und Lungenkrkh* 1996; **22** Suppl: S615-9.
- 107 WY1517. Bernard GR, Vincent JL, Laterre PF *et al.* Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001; **344**: 699-709.
- 108 WY1615. Cheng AC, Stephens DP, Currie BJ. Granulocyte-colony stimulating factor (G-CSF) as an adjunct to antibiotics in the treatment of pneumonia in adults (Review). *Cochrane Database of Systematic Reviews* 2004; CD004400.
- 109 WY956. Wunderink RG, Leeper KV, Schein R *et al.* Filgrastim in patients with pneumonia and severe sepsis or septic shock. *Chest* 2001; **119**: 523-29.
- 110 WY955. Meyanci G, Oz H. Combination of granulocyte colony-stimulating factor and antibacterial drugs for the treatment of ventilatory associated nosocomial pneumonia. *Middle East J Anesthesiol* 2001; **16**: 91-101.
- 111 WY954. Root RK, Lodato RF, Patrick W *et al.* Multicenter, double-blind, placebo-controlled study of the use of filgrastim in patients hospitalized with pneumonia and severe sepsis. *Crit Care Med* 2003; **31**: 367-73.
- 112 WY1009. Hartmann P, Lammertink J, Mansmann G *et al.* A randomized, placebo-controlled study of the use of filgrastim in non neutropenic patients with nosocomial pneumonia. *Eur J Med Res* 2005; **10**: 29-35.
- 113 WY631. Graham WG, Bradley DA. Efficacy of chest physiotherapy and intermittent positive-pressure breathing in the resolution of pneumonia. *N Engl J Med* 1978; **299**: 624-7.
- 114 WY652. Monton C, Ewig S, Torres A *et al.* Role of glucocorticoids on inflammatory response in nonimmunosuppressed patients with pneumonia: a pilot study. *Eur Respir J* 1999; **14**: 218-20.
- 115 WY644. Patterson TF, Patterson JE, Masecar BL *et al.* A nosocomial outbreak of *Branhamella catarrhalis* confirmed by restriction endonuclease analysis. *J Infect Dis* 1988; **157**: 996-1001.