Occasional review

Prevention of nosocomial bacterial pneumonia

Jean-Louis Vincent

The term "nosocomial pneumonia" broadly covers all infections occurring 48 hours or more after hospital admission excluding any infection incubating at the time of admission, and has also been called hospital acquired pneumonia. Intensive care unit (ICU) acquired pneumonia (occurring within 48 hours of admission to the ICU) and ventilator associated pneumonia (occurring within 48 hours of starting mechanical ventilation) are also included in the broader term "nosocomial pneumonia". The development of nosocomial pneumonia remains a major problem in the ICU with most studies reporting an incidence of between 9% and 45%,[1–19] depending on the groups of patients being studied, the definition of nosocomial pneumonia, and the criteria used to diagnose it. It has been shown that nosocomial pneumonia acquired in the ICU markedly increases the length of hospital stay[12 16 20 21] and the costs of hospital care.[21 22] Mortality rates may also be increased,[3 5 7 16 17 19 23] although it is not entirely clear whether all deaths from nosocomial pneumonia are directly related to the development of an infection. The so-called "attributable mortality", defined as the mortality occurring as the direct result of the nosocomial pneumonia, may be especially high when *Pseudomonas* or *Acinetobacter* species are involved as pathogens.[19]

The diagnosis of nosocomial pneumonia is not straightforward, particularly in patients who are critically ill, as routine parameters do not have a high specificity for pneumonia in these patients.[24] For example, infiltrates on chest radiographs consistent with pneumonia may be due to many other processes including oedema, atelectasis, and infarction.[25] Positive cultures from tracheal aspirates are also non-specific as the upper respiratory tract of most critically ill patients is colonised by potential pulmonary pathogens.[26] Alternative diagnostic techniques such as protected specimen brush biopsies and bronchoalveolar lavage have therefore been used, although a recent pilot study[27] suggested that complicated culture sampling using these techniques has no beneficial therapeutic influence over more simple endotracheal aspirate cultures. The various methods employed in the diagnosis of nosocomial pneumonia have been reviewed elsewhere.[28 29] This review focuses on methods of preventing the development of bacterial nosocomial pulmonary infections.

Department of Intensive Care, Erasme University Hospital, Free University of Brussels, B-1070 Belgium
J-L Vincent

Correspondence to:
Professor J-L Vincent.

Received 13 August 1998
Returned to author
6 October 1998
Revised manuscript received
26 November 1998
Accepted for publication
6 January 1999

Pathogenesis of nosocomial pneumonia

For a nosocomial pneumonia to occur, one or both of the following factors must be present: (1) the lower respiratory tract must be invaded by bacteria in sufficient numbers or of particular virulence and (2) pulmonary and systemic host defences must be downregulated.

With the high costs of nosocomial pulmonary pneumonia and the associated increased mortality, measures to prevent the development of such infections are important and can be considered in two groups—those aimed at preventing colonisation and those aimed at increasing host defences (table 1).

Prevention of colonisation

Colonisation of the upper respiratory tract is common in critically ill patients and may precede the development of nosocomial pneumonia. Measures to prevent colonisation are thus important in limiting nosocomial pneumonia. Infecting organisms may originate from external (exogenous) sources or from the patient's own flora (endogenous sources). Bacterial entry into the lungs from exogenous sources may occur by various routes including the aspiration of bacteria from the environment (transmitted, for example, on the hands of staff) or direct penetration (for example, via the pleural space). Entry from the endogenous pool of organisms may occur by aspiration from the oesophageal/gastric contents or by haematogenous spread—for example, from the gut by translocation or from a distant site of infection such as an infected catheter. An important early pathogenetic event in colonisation is the adherence of bacteria to the epithelium of the respiratory tract.[30] This bacterial adherence is influenced by alterations in the epithelial cells, bacterial surface characteristics, and exoproducts. The reduced mucociliary clearance and impaired local host immune responses commonly seen in critically ill patients facilitate increased colonisation.[31]

HYGIENE

The bacteria involved in nosocomial infections are frequently transmitted from the environment or from patient to patient on the hands of health care staff. Hand washing has long been recognised as an effective method of preventing this transfer of bacteria from the environment to the patient,[28 32] yet such a simple technique is frequently under-performed.[33 34] The use of an antimicrobial hand washing agent may be more

Table 1 Proposed strategies to prevent pulmonary nosocomial infections

Strategy	*Relative importance*	*Comments*
Preventing colonisation		
Hygiene	+++	Anti-microbial soaps may be more effective than non-medicated (prospective multiple crossover trial)
Heat and moisture exchangers	++	Reduced incidence of nosocomial pneumonia (randomised trial, meta-analysis) but caution as increased endotracheal secretions (randomised trial)
Selective digestive decontamination	++ (especially in trauma patients)	Reduced respiratory tract infections (meta-analysis) but risk of bacterial resistance remains a problem (prospective survey)
Subglottic drainage	++	Reduced incidence of nosocomial pneumonia (randomised trial, meta-analysis)
Semi-recumbent position	++	Reduces aspiration of gastric contents (randomised crossover trial)
Avoidance of H_2 blockers	+	May be of some benefit in reducing nosocomial pneumonia (meta-analysis) but increased risk of gastrointestinal bleeding
Kinetic beds	+	Reduces incidence of nosocomial pneumonia (randomised controlled trial) but not well tolerated by some patients
Influencing host response		
Early enteral nutrition	+++	Reduces risk of infection (meta-analysis); jejunal feeding may be preferable (randomised trial); immune supplemented feeds may provide more protection (randomised trial)
Cytokine administration	?	Remains experimental

effective than a non-medicated soap,[34] and the use of disposable gowns and aprons during patient contact may also be an effective means of limiting the transfer of organisms from the environment.[35]

VENTILATOR EQUIPMENT

Although transmission of bacteria via the respirator equipment was identified as a cause of pulmonary infections more than 15 years ago, recent studies have played down the importance of transmission of bacteria via the respiratory circuitry. Current systems are rarely a major source of bacteria. The use of sterile water in the humidifier reservoir, in particular, has significantly reduced the likelihood of bacterial colonisation of ventilator equipment. The frequency of ventilator circuit change has not been shown to influence the rate of infection[2 36] and, similarly, the use of closed suction systems has not been shown to be beneficial.[37] It has been suggested that the use of heat and moisture exchangers may reduce the rate of infection[38] but this remains a controversial issue as these systems have other problems including an increase in airway resistance associated with the accumulation of tracheal secretions in the system.[39 40]

SELECTIVE DIGESTIVE DECONTAMINATION (SDD)

The use of SDD has been based on the hypothesis of "colonisation resistance" in which anaerobic flora is considered to protect against the excessive growth of Gram negative bacteria. The systematic use of topical mixtures of antibiotics (usually polymyxin, tobramycin and amphotericin B) applied to the oropharynx and stomach, together with the intravenous administration of cefotaxime, has been shown to reduce the incidence of nosocomial pneumonia,[41–44] although not all studies have confirmed this finding.[8 45] A recent meta-analysis[46] did conclude that SDD can reduce respiratory tract infections and overall mortality in critically ill patients but, in view of the risk of bacterial resistance,[47] the systemic SDD approach has not gained widespread acceptance. Nevertheless, the use of SDD may be appropriate in particular clinical conditions including immunosuppressed patients and those undergoing liver transplantation and oesophagectomy. The topical use of antibiotics in the respiratory tract cannot be recommended.[28]

INAPPROPRIATE ANTIBIOTIC THERAPY

It has been clearly shown that the prior administration of antibiotics contributes to the development of nosocomial pneumonia and increases mortality.[23] However, inadequate early antibiotic coverage in nosocomial pneumonia is also associated with increased mortality.[48] It is therefore important to be rational in our choice and use of antibiotics, restricting excessive and inappropriate use. Each patient should be assessed individually as to his/her need for antibiotics and, when treatment is necessary, the antibiotic regime should be carefully selected according to the likely pathogen(s) and local resistance patterns.

MAINTENANCE OF LOW GASTRIC PH

H_2-blockers and antacids are frequently used in patients in the ICU to prevent the development of stress ulcers and bleeding. However, these agents raise intragastric pH which may enhance the colonisation of the stomach by Gram negative bacteria and thereby contribute to the development of nosocomial pneumonia. The evidence on the effects of H_2-antagonists on the development of nosocomial pneumonia is conflicting with some studies reporting a definite increased incidence[49] and others reporting no increased risk[50 51] of nosocomial pneumonia. In a meta-analysis of the literature Cook *et al*[52] concluded that there was a trend towards an increased risk of pneumonia in patients treated with H_2-receptor antagonists. In view of this

potential increased risk of pneumonia related to the effects of H_2-blockers on gastric pH, sucralfate has sometimes been preferred and, indeed, several meta-analyses of the literature have concluded that there is a reduced incidence of pneumonia in patients treated with sucralfate compared with H_2-blockers or antacids.[52–54] However, this has been a controversial issue. For instance, in the EPIC study[7] the type of gastric protective strategy did not seem to influence the development of pulmonary infections, a finding supported by several other studies.[55 56] These differences may be explained partly by the results of a study by Thomason *et al*[57] who found that the incidence of early onset pneumonia—that is, during the first four days of stress ulcer prophylaxis—was the same with sucralfate, antacid or H_2-blocker but that there was a trend towards a reduced incidence of pneumonia in the sucralfate group after four days of treatment. Further fuelling this controversy, a recent study by Cook *et al*[58] has shown that sucralfate provides less efficient anti-ulcer prophylaxis than H_2-antagonists, with no difference in the rate of ventilator associated pneumonia between the two groups. We can conclude from the available evidence that the use of H_2-receptor antagonists may increase the risk of nosocomial pneumonia and their systematic use in all patients is not warranted. However, despite the potential increased risk of pneumonia, when an anti-ulcer prophylactic strategy is necessary H_2-blockers are preferable to sucralfate for their superior anti-ulcer efficacy.

INTUBATION

The use of intubation via the nasal route may predispose to nosocomial sinusitis[59] which has been associated with the development of nosocomial pneumonia,[60] so oral intubation is preferred whenever possible. Torres *et al*[61] have shown that endotracheal re-intubation may be an important risk factor in the development of ventilator associated pneumonia, and care should therefore be taken before deciding on endotracheal extubation to avoid the possible need for re-intubation.

SUBGLOTTIC DRAINAGE OF SECRETIONS

Aspiration of the secretions accumulating above the inflated endotracheal cuff may be helpful in preventing colonisation of the lung. Special endotracheal tubes have been developed which have a separate lumen open to the subglottic region to allow continuous aspiration of these secretions. Studies on the effects of these tubes have reported a reduced incidence of nosocomial pneumonia.[62 63]

ROLE OF THE NASOGASTRIC TUBE

Duodenal reflux of gastric secretions may contribute to lung colonisation,[64] and it has been suggested that placement of a nasogastric tube in the stomach may facilitate the passage of bacteria from the gut into the airways, and hence be a risk factor for the development of pneumonia.[14] Some investigators have proposed using a small rather than a large nasogastric tube,[65] and others have suggested bypassing the stomach by using a jejunal tube instead of a gastric tube.[66] These issues are, however, still controversial and require further study before definite recommendations can be made regarding the use of the nasogastric tube.

AVOIDANCE OF EXCESSIVE SEDATION

Numerous studies have shown that coma and an altered level of consciousness can significantly contribute to the development of lung infections.[1 6 14 15 67] Accordingly, sedative agents should be titrated to the individual patient using, for example, a sedation score. By this means the use of excessive sedation could be reduced.

SEMI-RECUMBENT POSITION

It may be helpful to place patients in the ICU at risk of developing nosocomial pneumonia in the semi-recumbent position rather than supine to limit the passage of bacteria into the airways.[68] The supine position has been associated with an increased incidence of nosocomial pneumonia.[23] The use of kinetic beds has also been proposed to limit the risks of lung colonisation and reduce the incidence of nosocomial pneumonia.[69 70]

Modulating host defence

The host defence response is frequently impaired in critically ill patients, making them more prone to develop nosocomial infections. In the lungs the endotracheal tube bypasses host defences above the vocal cords and impairs lower respiratory tract defences such as cough and mucociliary clearance.[28] Systemic host defence is reduced in the presence of chronic illness, malnutrition, prolonged surgery, and various co-morbid illnesses such as respiratory failure. Reducing factors which limit host response and administering agents to modulate host defence directly may prevent nosocomial pneumonia.

IMMUNOSUPPRESSIVE AGENTS

Immunosuppressive agents such as corticosteroids and cytotoxic agents impair various host defence mechanisms including gut barrier function,[71] and immunosuppression has been identified as a risk factor for nosocomial pneumonia in children.[72] Immunosuppressive agents should thus be avoided wherever possible and, when necessary, the minimal effective dose should be used and treatment should be regularly reviewed and stopped at the earliest opportunity.

NUTRITIONAL SUPPORT

By impairing host defence, malnutrition has been shown to be a major contributing factor to the development of pneumonia.[28 65 73] Providing adequate nutritional support to intensive care patients is thus important in the prevention of nosocomial pneumonia, although the preferred route of administration and the nature of the feeds has been subject to debate. Enteral nutrition, particularly given early, is generally preferred to parenteral feeding and is associated with fewer septic complications.[74] However, by raising the pH in the stomach, enteral feeds may encourage bacterial colonisa-

tion and hence increase the risk of pneumonia. Montecalvo *et al*[66] therefore suggested the use of jejunal feeding tubes to bypass the stomach and, in a small group of ICU patients, this technique was found to reduce the incidence of nosocomial pneumonia and improve the nutritional status compared with gastric fed patients. Recently, the use of immune enhancing feeds enriched with a variety of nutrients including amino acids, arginine, glutamine, and nucleotides has been associated with fewer acquired infections.[75] Further studies are needed to determine the precise combination of nutrients which will provide the most beneficial effects but early enteral nutrition to stimulate gut immunological function should be provided to patients in intensive care, initially supplemented by parenteral nutrition when enteral nutrition can only be tolerated in low volumes.[74]

ADMINISTRATION OF CYTOKINES TO ENHANCE HOST DEFENCE

As immunosuppression is a major factor in the development of nosocomial pneumonias,[72] the restoration of an adequate immune response may represent an important strategy to prevent nosocomial lung infections. Docke *et al*[76] have recently shown that the administration of interferon-γ (IFN-γ) may restore monocyte function, although clinical studies of the effects of prophylactic systemic IFN-γ on infection rates are inconclusive.[77 78] Local aerosol administration of IFN-γ may be an effective means of augmenting local host defences[79] but this has not been assessed in clinical trials. Interleukin-12 (IL-12), a pro-inflammatory cytokine, can stimulate the Th-1 type immune responses and the administration of IL-12 has been shown to protect animals against lung infections.[80] The administration of granulocyte colony stimulating factor (G-CSF) may also have a role in the prevention of nosocomial infections. Animals without G-CSF are less able to resist infection,[81] and the administration of G-CSF to patients at risk of developing pneumonia may prove beneficial. However, a recent randomised, placebo controlled, clinical study[82] using prophylactic G-CSF in patients with acute traumatic brain injury or cerebral haemorrhage reported no difference in the incidence of nosocomial pneumonia compared with placebo treated patients. Prophylactic immunomodulating agents represent an exciting area of ongoing research but many more studies are required before any recommendations can be made regarding their routine use in intensive care patients.

Conclusion

Nosocomial pneumonia poses a considerable load in terms of morbidity, mortality, and cost in the ICU. The prevention of such infections is therefore of considerable clinical and economic interest. A number of measures aimed at reducing the occurrence of nosocomial pneumonia have been suggested and investigated. Some methods, such as hand washing, have been unequivocally proved to be beneficial and should be a routine part of ICU patient care. The overzealous use of antibiotics and the administration of excessive sedative agents should certainly be discouraged. Oral intubation and, if possible, placing patients in the semi-recumbent position rather than supine are also important factors in preventing nosocomial pneumonia. Other methods are more controversial and cannot be routinely recommended. H_2-blockers are of little value in reducing the incidence of nosocomial pneumonia and SDD is of benefit only in certain groups of patients. The administration of immunosuppressive agents should be kept to a minimum as these further reduce host defence. Early enteral nutrition should be administered, supported by parenteral nutrition in the early stages if enteral tolerance is poor. Immune supplemented feeds may prove to be of greater benefit but further studies are needed. The possibility of stimulating the immune response in its fight against infection is an exciting area of active research, but immunomodulating agents remain at the experimental stage at the present time.

The appropriate use of some of the techniques discussed can certainly reduce the incidence of nosocomial pneumonia in some of the patients in the ICU. While simple methods such as hand washing should be part of routine practice, the use of predictive models to identify patients at high risk of nosocomial pneumonia can help us to focus other, more invasive, preventative measures on those most likely to benefit.[6 14] The results of ongoing research, particularly into techniques to modulate immune defence, may strengthen our preventative capabilities and help to limit further the number of patients who currently develop nosocomial pneumonia.

1 Chevret S, Hemmer M, Carlet J, *et al*. Incidence and risk factors of pneumonia acquired in intensive care units. *Intensive Care Med* 1993;**19**:256–64.
2 Dreyfuss D, Djedaini K, Weber P, *et al*. Prospective study of nosocomial pneumonia and of patient and circuit colonization during mechanical ventilation with circuit changes every 48 hours versus no change. *Am Rev Respir Dis* 1991; **143**:738–43.
3 Kollef MH, Silver P, Murphy DM, *et al*. The effect of late-onset ventilator associated pneumonia in determining patient mortality. *Chest* 1995;**108**:1655–62.
4 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.
5 Fagon JY, Chastre J, Vuagnat A, *et al*. Nosocomial pneumonia and mortality among patients in intensive care units. *JAMA* 1996;**275**:866–9.
6 Kropec A, Schulgen G, Just H, *et al*. Scoring systems for nosocomial pneumonia in ICUs. *Intensive Care Med* 1996; **22**:1155–61.
7 Vincent JL, Bihari D, Suter PM, *et al*. The prevalence of nosocomial infection in intensive care units in Europe: the results of the EPIC study. *JAMA* 1995;**274**:639–44.
8 Wiener J, Itokazu G, Nathan C, *et al*. A randomized, double-blind, placebo-controlled trial of selective digestive decontamination in a medical-surgical intensive care unit. *Clin Infect Dis* 1995;**20**:861–7.
9 Albert S, Kirchner J, Thomas H, *et al*. Role of quantitative cultures and microscopic examinations of endotracheal aspirates in the diagnosis of pulmonary infections in ventilated patients. *J Hosp Infect* 1997;**37**:25–37.
10 Marsh B, Hone R, White M, *et al*. European Nosocomial Infection Survey: analysis of Irish data. *Ir Med J* 1996;**89**:96–8.
11 Denys D, Martens P, Mullie A, *et al*. Incidence of nosocomial pneumonia in ICU patients. *Acta Anaesthesiol Belg* 1993;**44**:111–8.
12 Rello J, Quintana E, Ausina V, *et al*. Incidence, etiology and outcome of nosocomial pneumonia in mechanically ventilated patients. *Chest* 1991;**100**:439–44.
13 Rello J, Ausina V, Ricart M, *et al*. Nosocomial pneumonia in critically ill comatose patients: need for a differential therapeutic approach. *Eur Respir J* 1992;**5**:1249–53.
14 Joshi N, Localio AR, Hamory BH. A predictive risk index for nosocomial pneumonia in the intensive care unit. *Am J Med* 1992;**93**:135–42.

15 Rello J, Ausina V, Castella J, *et al*. Nosocomial respiratory tract infections in multiple trauma patients. Influence of level of consciousness with implications for therapy. *Chest* 1992;**102**:525–9.
16 Nielsen SL, Roder B, Magnussen P, *et al*. Nosocomial pneumonia in an intensive care unit in a Danish university hospital: incidence, mortality and etiology. *Scand J Infect Dis* 1992;**24**:65–70.
17 Torres A, Aznar R, Gatell JM, *et al*. Incidence, risk and prognosis factors of nosocomial pneumonia in mechanically ventilated patients. *Am Rev Respir Dis* 1990;**142**:523–8.
18 Craven DE, Kunches LM, Lichtenberg DA, *et al*. Nosocomial infection and fatality in medical and surgical intensive care unit patients. *Arch Intern Med* 1988;**148**:1161–8.
19 Fagon JY, Chastre J, Hance AJ, *et al*. Nosocomial pneumonia in ventilated patients: a cohort study evaluating attributable mortality and hospital stay. *Am J Med* 1993;**94**:281–8.
20 Leu HS, Kaiser DL, Mori M, *et al*. Hospital-acquired pneumonia. Attributable mortality and morbidity. *Am J Epidemiol* 1989;**129**:1258–67.
21 Kappstein I, Schulgen G, Beyer U, *et al*. Prolongation of hospital stay and extra costs due to ventilator-associated pneumonia in an intensive care unit. *Eur J Clin Microbiol Infect Dis* 1992;**11**:504–8.
22 Baker AM, Meredith JW, Haponik EF. Pneumonia in intubated trauma patients. Microbiology and outcomes. *Am J Respir Crit Care Med* 1996;**153**:343–9.
23 Kollef MH. Ventilator-associated pneumonia. A multivariate analysis. *JAMA* 1993;**270**:1965–70.
24 Bonten MJ, Gaillard CA, van Tiel FH, *et al*. The stomach is not a source for colonization of the upper respiratory tract and pneumonia in ICU patients. *Crit Care Med* 1994;**105**: 878–84.
25 Wunderink RG, Woldenberg LS, Zeiss J, *et al*. The radiologic diagnosis of autopsy-proven ventilator-associated pneumonia. *Chest* 1992;**101**:458–63.
26 Geddes DM. Infection versus colonisation. *Intensive Care Med* 1990;**16**:S201–5
27 Sanchez-Nieto JM, Torres A, Arcia-Cordoba F, *et al*. Impact of invasive and non-invasive quantitative culture sampling on outcome of ventilator-associated pneumonia. *Am J Respir Crit Care Med* 1998;**157**:371–6.
28 American Thoracic Society. Hospital-acquired pneumonia in adults: diagnosis, assessment of severity, initial antimicrobial therapy and preventative strategies. *Am J Respir Crit Care Med* 1995;**153**:1711–25.
29 Fagon JY, Chastre J. Diagnosis of nosocomial pneumonia in intensive care unit patients. *Curr Opin Crit Care* 1997;**3**: 363–9.
30 Cassiere HA, Niederman MS. New etiopathogenic concepts of ventilator-associated pneumonia. *Semin Respir Infect* 1996;**11**:13–23.
31 Niederman MS. Gram-negative colonization of the respiratory tract: pathogenesis and clinical consequences. *Semin Respir Infect* 1990;**5**:173–84.
32 Steere AC, Mallison GF. Handwashing practices for the prevention of nosocomial infections. *Ann Intern Med* 1975; **83**:683–90.
33 Graham M. Frequency and duration of handwashing in an intensive care unit. *Am J Infect Control* 1990;**18**:77–81.
34 Doebbeling BN, Stanley GL, Sheetz CT, *et al*. Comparative efficacy of alternative hand-washing agents in reducing nosocomial infections in intensive care units. *N Engl J Med* 1992;**327**:88–93.
35 Crowe M, Towner KJ, Humphreys H. Clinical and epidemiological features of an outbreak of acinetobacter infection in an intensive therapy unit. *J Med Microbiol* 1995;**43**:55–62.
36 Long MN, Wickstrom G, Grimes A, *et al*. Prospective, randomized study of ventilator-associated pneumonia in patients with one versus three ventilator circuit changes per week. *Infect Control Hosp Epidemiol* 1996;**17**:14–9.
37 Deppe SA, Kelly JW, Thoi LL, *et al*. Incidence of colonization, nosocomial pneumonia and mortality in critically ill patients using a Trach Care closed-suction system versus an open-suction: prospective, randomized study. *Crit Care Med* 1990;**18**:1389–93.
38 Kirton OC, DeHaven BMJ, Morejon O, *et al*. A prospective, randomized comparison of an in-line heat moisture exchange filter and heated wire humidifiers: rates of ventilator-associated early onset (community acquired) or late-onset (hospital-acquired) pneumonia and incidence of endotracheal tube occlusion. *Chest* 1997;**112**:1055–9.
39 Cohen IL, Weinberg PF, Fein IA, *et al*. ET tube occlusion associated with the use of heat and moisture exchangers in the intensive care unit. *Crit Care Med* 1988;**16**:277–9.
40 Martin C, Perrin G, Gevaudan M, *et al*. Heat and moisture exchangers and vaporizing humidifiers in the ICU. *Chest* 1990;**97**:144–9.
41 Abele-Horn M, Dauber A, Bauernfeind A, *et al*. Decrease in nosocomial pneumonia in ventilated patients by selective oropharyngeal decontamination. *Intensive Care Med* 1997; **23**:187–95.
42 Vandenbroucke-Grauls CM, Vandenbroucke JP. Effect of selective decontamination of the digestive tract on respiratory tract infections and mortality in the intensive care unit. *Lancet* 1991;**338**:859–62.
43 Rogers CJ, van Saene HK, Suter P, *et al*. Infection control in critically ill patients: effects of selective contamination of the digestive tract. *Am J Hosp Pharmacol* 1994;**51**:631–48.
44 Cockerill FRI, Muller SR, Ahnalt JP, *et al*. Prevention of infection in critically ill patients by selective decontamination of the digestive tract. *Ann Intern Med* 1992;**117**:545–53.
45 Hammond JM, Potgieter PD, Saunders GL, *et al*. Double-blind study of selective decontamination of the digestive tract in intensive care. *Lancet* 1992;**340**:5–9.
46 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.
47 Nardi G, Valentinis U, Proietti A, *et al*. Epidemiological impact of prolonged systematic use of topical SDD on bacterial colonization of the tracheobronchial tree and antibiotic resistance. *Intensive Care Med* 1993;**19**:273–8.
48 Kollef MH, Ward S. The influence of mini-BAL cultures on patients outcomes: implications for the antibiotic management of ventilator-associated pneumonia. *Chest* 1998;**113**: 412–20.
49 Apte NM, Karnad DR, Medhekar TP, *et al*. Gastric colonization and pneumonia in intubated critically ill patients receiving stress ulcer prophylaxis: a randomized, controlled trial. *Crit Care Med* 1992;**20**:590–3.
50 Martin LF, Booth FV, Karlstadt RG, *et al*. Continuous intravenous cimetidine decreases stress-related gastrointestinal hemorrhage without promoting pneumonia. *Crit Care Med* 1993;**21**:19–30.
51 Metz CA, Livingston DH, Smith JS, *et al*. Impact of multiple risk factors and ranitidine prophylaxis on the development of stress-related gastrointestinal bleeding: a prospective, multicenter, double-blind, randomized trial. *Crit Care Med* 1993;**21**:1844–9.
52 Cook DJ, Reeve BK, Guyatt GH, *et al*. Stress ulcer prophylaxis in critically ill patients. *JAMA* 1996;**275**:308–14.
53 Tryba M. Sucralfate versus antacids or H_2-antagonists for stress ulcer prophylaxis: a meta-analysis on efficacy and pneumonia rate. *Crit Care Med* 1991;**19**:942–9.
54 Cook DJ, Laine LA, Guyatt GH, *et al*. Nosocomial pneumonia and the role of gastric pH. A meta-analysis. *Chest* 1991;**100**:7–13.
55 Bonten MJ, Gaillard CA, van der Geest S, *et al*. The role of intragastric acidity and stress ulcer prophylaxis on colonization and infection in mechanically ventilated ICU patients. A stratified, randomized, double-blind study of sucralfate versus antacids. *Am J Respir Crit Care Med* 1995; **152**:1825–34.
56 Ben-Menachem T, Fogel R, Patel RV, *et al*. Prophylaxis for stress-related gastric hemorrhage in the medical intensive care unit. A randomized, controlled, single-blind study. *Ann Intern Med* 1994;**121**:568–75.
57 Thomason MH, Payseur ES, Hakenewerth AM, *et al*. Nosocomial pneumonia in ventilated trauma patients during stress ulcer prophylaxis with sucralfate, antacid and ranitidine. *J Trauma* 1996;**41**:503–8.
58 Cook D, Guyatt G, Marshall J, *et al*. A comparison of sucralfate and ranitidine for the prevention of upper gastrointestinal bleeding in patients requiring mechanical ventilation. *N Engl J Med* 1998;**338**:791–7.
59 Sinuff T, Cook DJ. Nosocomial sinusitis: a critical appraisal of the evidence. In: Vincent JL, ed. *Yearbook of intensive care and emergency medicine*. Heidelberg: Springer-Verlag, 1998: 292–9.
60 Holzapfel L, Chevret S, Madinier G, *et al*. Influence of long-term oro- or nasotracheal intubation on nosocomial maxillary sinusitis and pneumonia: results of a prospective, randomized, clinical trial. *Crit Care Med* 1993;**21**:1132–8.
61 Torres A, Gatell JM, Aznar E, *et al*. Re-intubation increases the risk of nosocomial pneumonia in patients needing mechanical ventilation. *Am J Respir Crit Care Med* 1995;**152**:137–41.
62 Mahul P, Auboyer C, Jospe R, *et al*. Prevention of nosocomial pneumonia in intubated patients: respective role of mechanical subglottic secretions and stress ulcer prophylaxis. *Intensive Care Med* 1992;**18**:20–5.
63 Valles J, Artigas A, Rello J, *et al*. Continuous aspiration of subglottic secretions in preventing ventilator-associated pneumonia. *Ann Intern Med* 1995;**122**:179–86.
64 Inglis TJ, Sherratt MJ, Sproat LJ, *et al*. Gastroduodenal dysfunction and bacterial colonisation of the ventilated lung. *Lancet* 1993;**341**:911–3.
65 Vallés J. Severe pneumonia: sources of infection and implications for treatment. *Sepsis* 1998;**1**:199–209.
66 Montecalvo MA, Steger KA, Farber HW, *et al*. Nutritional outcome and pneumonia in critical care patients randomized to gastric versus jejunal tube feedings. *Crit Care Med* 1992;**20**:1377–87.
67 Celis R, Torres A, Gatell JM, *et al*. Nosocomial pneumonia. A multivariate analysis of risk and prognosis. *Chest* 1988;**93**:318–24.
68 Torres A, Serra-Battles J, Ros E, *et al*. Pulmonary aspiration of gastric contents in patients receiving mechanical ventilation: the effect of body position. *Ann Intern Med* 1992;**116**:540–3.
69 Whiteman K, Nachtmann L, Kramer D, *et al*. Effects of continuous lateral rotation therapy on pulmonary complications in liver transplant patients. *Am J Crit Care* 1995;**4**: 133–9.
70 Cook D, De Jonghe B, Brochard L, *et al*. Influence of airway management on ventilator-associated pneumonia: evidence from randomized trials. *JAMA* 1998;**279**:781–7.
71 Gennari R, Alexander JW. Arginine, glutamine, and dehydroepiandrosterone reverse the immunosuppressive effect of prednisone during gut-derived sepsis. *Crit Care Med* 1997;**25**:1207–14.
72 Fayon MJ, Tucci M, Lacroix J, *et al*. Nosocomial pneumonia and tracheitis in a pediatric intensive care unit: a prospective study. *Am J Respir Crit Care Med* 1997;**155**:162–9.

73 Hanson LC, Weber DJ, Rutala WA, *et al*. Risk factors for nosocomial pneumonia in the elderly. *Am J Med* 1992;**92**: 161–6.
74 Heyland DK, Cook DJ, Guyatt GH. Enteral nutrition in the critically ill patient: a critical review of the evidence. *Intensive Care Med* 1993;**19**:435–42.
75 Bower RH, Cerra FB, Bershadsky B, *et al*. Early enteral administration of a formula (Impact) supplemented with arginine, nucleotides, and fish oil in intensive care unit patients: results of a multicenter, prospective, randomized, clinical trial. *Crit Care Med* 1995;**23**:436–49.
76 Docke WD, Randow F, Syrbe HP, *et al*. Monocyte deactivation in septic patients: restoration by IFN-γ treatment. *Nature Med* 1997;**3**:678–81.
77 Dries DJ, Jurkovich GJ, Maier RV, *et al*. Effect of interferon gamma on infection-related death in patients with severe injuries. A randomized, double-blind, placebo-controlled trial. *Arch Surg* 1994;**129**:1031–41.
78 Wasserman D, Ioannovish JD, Hinzmann RD, *et al*. Interferon-gamma in the prevention of severe burn-related infections: a European phase III multicenter trial. *Crit Care Med* 1998;**26**:434–9.
79 Beck JM, Liggitt HD, Brunette EN, *et al*. Reduction of intensity of *Pneumocystis carinii* pneumonia in mice by aerosol administration of gamma interferon. *Infect Immunol* 1991;**59**:3859–62.
80 Greenberger MJ, Kunkel SL, Strieter RM, *et al*. IL-12 gene therapy protects mice in lethal *Klebsiella* pneumonia. *J Immunol* 1996;**157**:3006–12.
81 Lieschke GJ, Grail D, Hodgson G, *et al*. Mice lacking granulocyte colony-stimulating factor have chronic neutropenia, granulocyte and macrophage progenitor cell deficiency, and impaired neutrophil mobilization. *Blood* 1994;**84**:1737–46.
82 Heard SO, Fink MP, Gamelli RL, *et al*. Effect of prophylactic administration of recombinant human granulocyte colony-stimulating factor (filgrastim) on the frequency of nosocomial infections in patients with acute traumatic brain injury or cerebral hemorrhage. *Crit Care Med* 1998;**26**:748–54.