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Review Article

Pharmaceutical strategies to prevent ventilator-associated pneumonia

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Abstract

The increasing incidence of hospital-acquired (nosocomial) infection is a disturbing phenomenon resulting in significant patient mortality and putting considerable strain on healthcare budgets and personnel. One particularly serious aspect of nosocomial infection is that of ventilator-associated pneumonia (VAP). This arises in patients who receive mechanical ventilation within the intensive care unit. The quoted incidence of VAP varies widely (5–67%) and the reported mortality of patients with VAP is in the range of 24–71%. This review will examine the many factors that account for these wide ranges reported, including the patient population under investigation, the causative organism, the method of diagnosis, interventions employed and preventative strategies. The use of bioactive and drug-impregnated biomaterials for endotracheal tube construction is discussed as novel approaches to the prevention of VAP.

Introduction

A recent study (Plowman et al 2000), commissioned by the Department of Health, estimated that hospital-acquired infection may cost the National Health Service in England almost £1 billion (£1000 million) a year and on this basis the National Audit Office (2000) estimated possible gross savings of £150 million a year, if preventative measures are established. It is accepted that of all nosocomial infection in the intensive care unit (ICU), pneumonia is the most commonly reported in mechanically ventilated patients (George 1995). Ventilator-associated pneumonia (VAP) refers to a subset of nosocomial pneumonia that arises in patients in whom the pneumonia was neither present nor incubating at intubation and who have been receiving mechanical ventilation via an endotracheal tube (Figure 1) for at least 48 h (Craven et al 1991; Mandell et al 1993).

Epidemiology

To date, there is no universally accepted gold standard for diagnosis of VAP (Chastre & Fagon 1994; Niedermann et al 1994), which hampers the understanding of the epidemiology of VAP and hence the formulation of more effective preventative measures. According to data from the National Nosocomial Infection Surveillance (NNIS) system (Horan et al 1986) and a UK prevalence study (Emmerson et al 1996), pneumonias are the second most common type of hospital-acquired infection after urinary tract infections. Vincent et al (1995) performed the largest intensive care unit (ICU) European prevalence study, which revealed that VAP caused almost half of ICU infections. Although patients receiving mechanical ventilation do not represent a major proportion of patients who have nosocomial pneumonia, they are at the greatest risk of acquiring the infection. Patients receiving mechanical ventilation are 6–21 times more likely to develop pneumonia than unventilated patients (Cross & Roup 1981; Celis et al 1988; Horan et al 1993; Chastre et al 1995; Fagon et al 1996). Cook et al (1998a) showed that the risk of developing VAP increased cumulatively with the duration of mechanical ventilation, with an overall rate of 14.8 cases per 1000 ventilator days. Interestingly the daily hazard rate decreased after day 5. Jarvis et al (1991) showed that the median rate of VAP ranged from 4.7 cases in paediatric ICUs to 34.4 cases in burn ICUs, per 1000 ventilator-days, whereas the median rate of non-VAP

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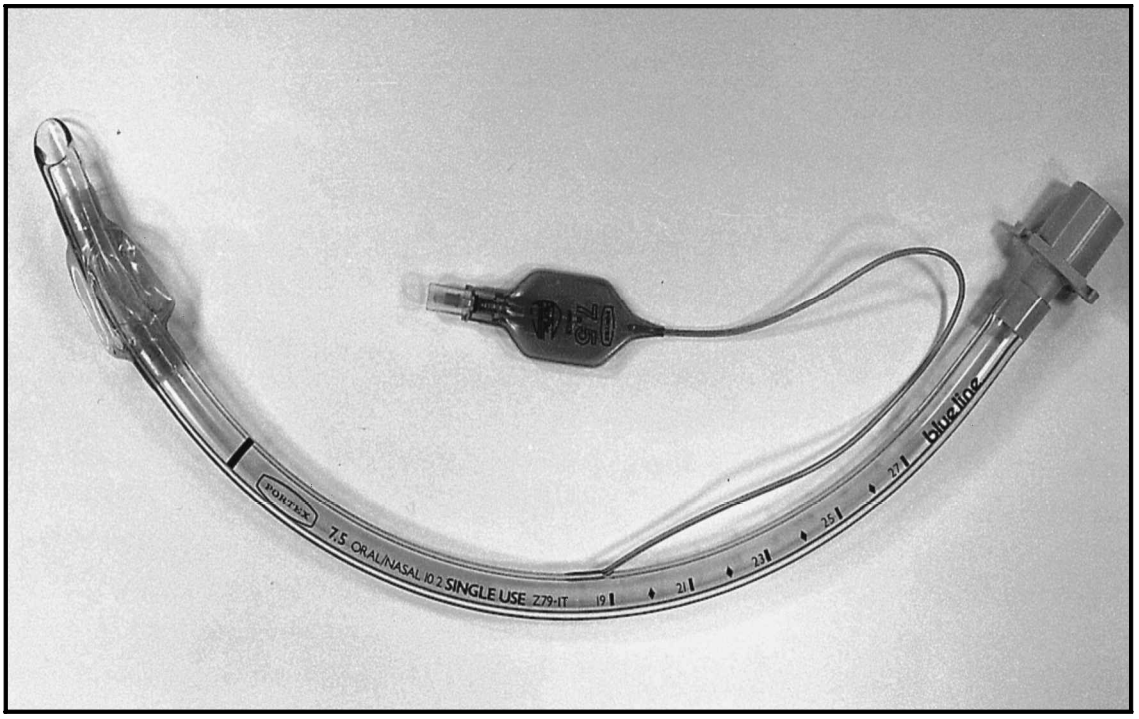

Figure 1 The endotracheal tube.

cases ranged from 0 cases in paediatric and respiratory ICUs to 3.2 cases in trauma ICUs per 1000 ICU-days. Within the published liteature, the incidence quoted for VAP varies widely, from 5–67% (Craven et al 1986; Kerver et al 1988; Fagon et al 1993; Kollef 1993; Baker et al 1996) due to several factors. These include: the population under investigation (e.g. severity of illness, case mix); causative microorganism (e.g. oropharyngeal flora, aerobic Gram-negative bacteria); interventions that change risk over time in the ICU (e.g. antibiotic exposure and various preventative strategies).

Methods used to diagnose VAP

Mortality and morbidity

There is a two- to ten-fold increase in mortality among ICU patients (Cross & Roup 1981; Craven et al 1986; Torres et al 1990). Reported crude mortality of patients with VAP ranges from 24% to 71%, depending on pathogen, type of ICU, diagnostic method utilised and extent of underlying disease (Craven et al 1986; Fagon et al 1989, 1993; Jimenez et al 1989; Ferrer et al 1994; Baker et al 1996). Fagon et al (1993) demonstrated the mortality rate attributable to VAP (at 27%) increased to 43% when the causative organism was *Pseudomonas aeruginosa* or *Acinetobacter* spp. Most studies report VAP as an independent risk factor for hospital mortality (Fagon et al 1993; Kollef et al 1997a; Ibrahim et al 2000; Bercault & Boulain 2001), although this is not universally accepted (Bregeon et al 2001). Other factors may be more important for patient outcomes in those where VAP, as well as other hospital-acquired infections, develop, as illustrated in Figure 2 (Wunderink 1998). For example, multiresistant microorganisms may explain the increased rate of death associated with VAP (Bercault & Boulain 2001), in which pneumonia due to drug-resistant bacteria was significantly associated with mortality.

Although debate persists about the mortality of VAP among other causes of death in critically ill patients, there is little doubt that VAP causes considerable morbidity by increasing the duration of mechanical ventilation, ICU stay and hospital care costs (Jimenez et al 1989; Heyland et al 1999). Heyland et al (1999), on evaluating 177 patients with VAP, demonstrated that such patients stayed in ICU 4.3 days longer than those matched patients who did not develop VAP. The ICU stay was longer for medical patients than surgical patients, and for patients infected with high-risk microorganisms than with low-risk microorganisms. In the largest case–control prevalence study to date of VAP (9080 patients) (Ollendorf et al 2001), it was shown that the incurred mean billed charges were US $40 000 higher than those of control patients without the condition.

Aetiology

The reported distribution of pathogens causing VAP is not uniform due to variability as summarised in Table 1. However, the majority of studies have been consistent in identifying Gram-negative bacteria, including *P. aeruginosa* and *Acinetobacter* spp, as the predominant pathogens causing 55–85% of VAP cases. Increasingly Gram-positive cocci, especially *Staphylococcus aureus*, is implicated in VAP, accounting for 20–40%, and 40–60% of

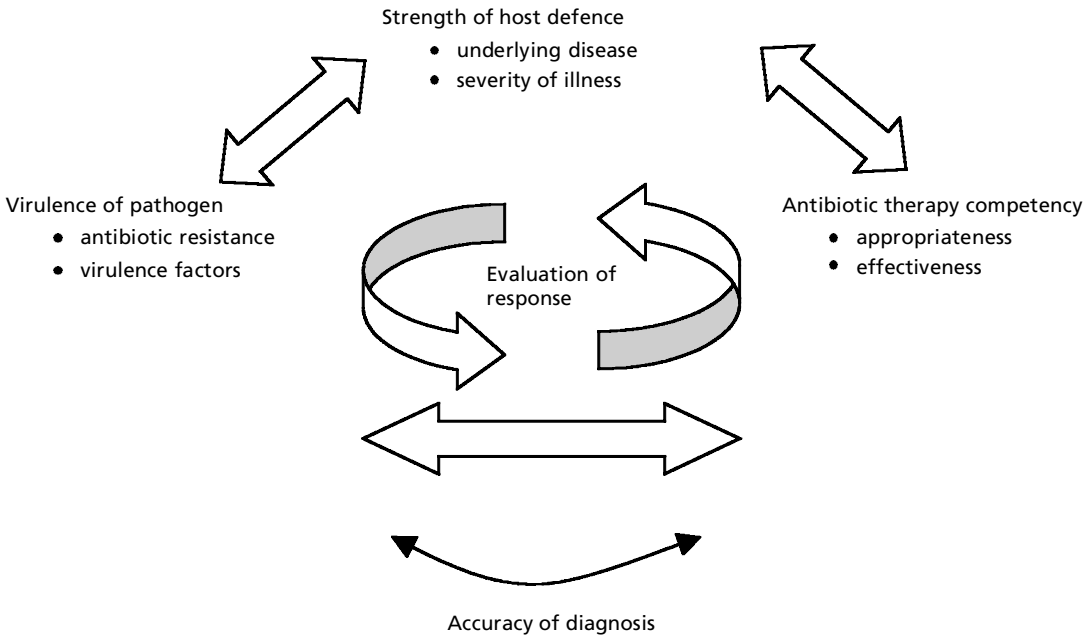

Figure 2 Factors affecting the mortality of VAP.

cases are polymicrobial (Fagon et al 1989; Torres et al 1990; Rello et al 1993; Baker et al 1996; Carver & Steger 1996; Chastre et al 1998; George et al 1998; Ewig et al 1999; Heyland et al 1999; Richards et al 1999). Although approximately 20% of all nosocomial pneumonia is attributable to viruses, data regarding VAP is limited, as is data on anaerobic infections. This may suggest an insignificant role in the aetiology of VAP. However, reporting hospitals do not routinely carry out anaerobic and viral cultures.

VAP can be divided into 2 groups (Pingleton et al 1992) – early-onset pneumonia and late-onset pneumonia. Early-onset pneumonia occurs during the 48–96 h after tracheal intubation and is commonly caused by antibiotic-sensitive bacteria such as methicillin-sensitive *S. aureus* (MSSA), *Haemophilus influenzae*, and *Streptococcus pneumoniae*. Late-onset pneumonia usually occurs at least four days after intubation and is often due to antibiotic-resistant pathogens such as methicillin-resistant *S. aureus* (MRSA), *P. aeruginosa, Acinetobacter* spp and *Enterobacter* spp.

Table 1 The causes of variation in the aetiology of VAP.

Hospital
ICU
Patient population
Antimicrobial usage
Diagnostic method used
Onset of VAP – early vs late
Length of hospital stay

In two studies, *P. aeruginosa* was not implicated in early-onset pneumonia but was the causative agent in 28% and 29% of late-onset pneumonia cases. Prod'hom et al (1994) demonstrated that in 54% of cases of early-onset pneumonia, pathogens implicated included *S. pneumoniae, H. influenzae*, or *S. aureus, w*hile George et al (1998) reported *S. pneumoniae* and *H. influenzae* as the pathogens involved in 25% of early-onset cases, but found them to be absent in late-onset cases.

Over the past 20 years antibiotic resistance has steadily increased worldwide. The NNIS system in the USA, operational since the 1970s, has revealed the emergence of some opportunistic pathogens in ICUs (e.g. *Acinetobacter*, MRSA, and *Enterobacter*). Overall, the most frequently isolated organisms are *S. aureus* (18.1%) and *P. aeruginosa* (17%). Results obtained from a European multicentre (1417 ICUs) study (Vincent et al 1995) found *Acinetobacter* to be more prevalent in Europe, while *Enterobacter* was more prevalent in the USA. It also found small differences in incidence between *S. aureus* (31.7%) and *P. aeruginosa* (29.8%) and confirmed an increasing number of Gram-positive infections, particularly coagulase-negative staphylococci.

Pathogenesis

In mechanically ventilated patients, when a sufficient concentration of pathogen reaches the lung parenchyma and overcomes the host defences, pneumonia results (Figure 3). The majority of cases of VAP appear to result from the aspiration of pathogens from potential colonised sources such as the upper aero-digestive tract (oropharynx, stomach, subglottal area and, possibly, infected maxillary sinuses), respiratory therapy equipment and ICU personnel (Craven & Steger 1995).

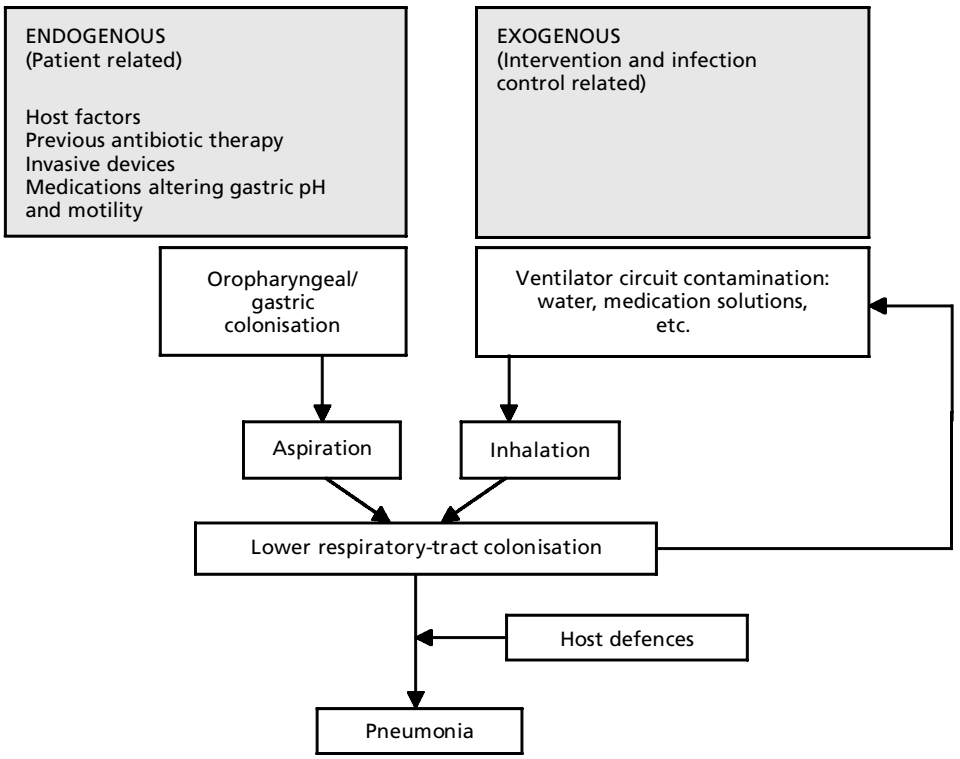

Figure 3 Schematic diagram of the pathogenesis of VAP.

Invasive medical devices have been cited as an important factor in the pathogenesis of VAP (Gorman & Jones 2003). The likelihood of aspiration is increased when a nasogastric tube is sited, predisposing the patient to gastric reflux. Endotracheal tubes assist the entry of bacteria into the tracheobronchial tree and aspiration into the lower airway of contaminated secretions by weakening the natural barrier between the oropharynx and trachea, the pooling and leakage of contaminated secretions above the endotracheal tube cuff, mucosal injury and the loss of the cough reflex (Craven & Steger 1995). Biofilm formation on the endotracheal tube (Figure 4) has also been implicated in the pathogenesis of VAP (Adair et al 1999, 2002).

On the whole, it is assumed that the occurrence of VAP is accompanied by increased mortality, longer duration of mechanical ventilation and longer stay in ICU with an increased use of antibiotics and higher associated healthcare costs (Craven & Steger 1995; Papazian et al 1996). Thus, the prevention of such infection has the highest priority, yet despite extensive scientific literature there is still no consensus as to how this goal should be achieved. Despite a wide range of preventative strategies for VAP (Kollef 1999), this review will focus on the pharmacological measures used to prevent VAP.

Stress-ulcer prophylaxis (SUP) regimen

Patients receiving mechanical ventilation are deemed to be at high risk for stress ulceration (Cook et al 1994) with the same authors reporting (Cook et al 1991a) a 4% incidence of bleeding in this population. The efficiency of various stress-ulcer prophylaxis (SUP) agents (Table 2) has been assessed in many studies but has produced inconsistent results. Thus, it is common practice for ICU patients to undergo SUP.

Agents routinely used as SUP include H_2-receptor antagonists and antacids that increase gastric pH. Neutralisation of the gastric juice encourages bacterial colonisation of the stomach, a potential reservoir for aerobic Gram-negative bacteria (Atherton & White 1978; Apte et al 1992; Prod'hom et al 1994) and may be an important source of pathogens that contribute to VAP. Sucralfate, a non-absorbable aluminium salt of sucrose octasulfate, forms a protective layer over ulcers and binds pepsin and bile acids and has little or no effect on gastric pH or secretion. It is on this basis that sucralfate, by not elevating gastric pH, does not cause bacterial overgrowth (Ephgrave et al 1998) and may help prevent VAP. Sucralfate in-vitro demonstrates antibacterial action against *Escherichia coli* and *P. aeruginosa* (Tryba & Mantey-Stiers 1987). It also interacts with drugs, such as phenytoin, fluoroquinolones, tetracycline and digoxin, to reduce their oral bioavailability.

Many studies (Driks et al 1987; Laggner et al 1989; Eddleston et al 1991; Maier et al 1994; Prod'hom et al 1994; Mustafa et al 1995) suggested that the use of sucralfate was associated with lower incidences of VAP. However Prod'hom et al (1994) observed that sucralfate

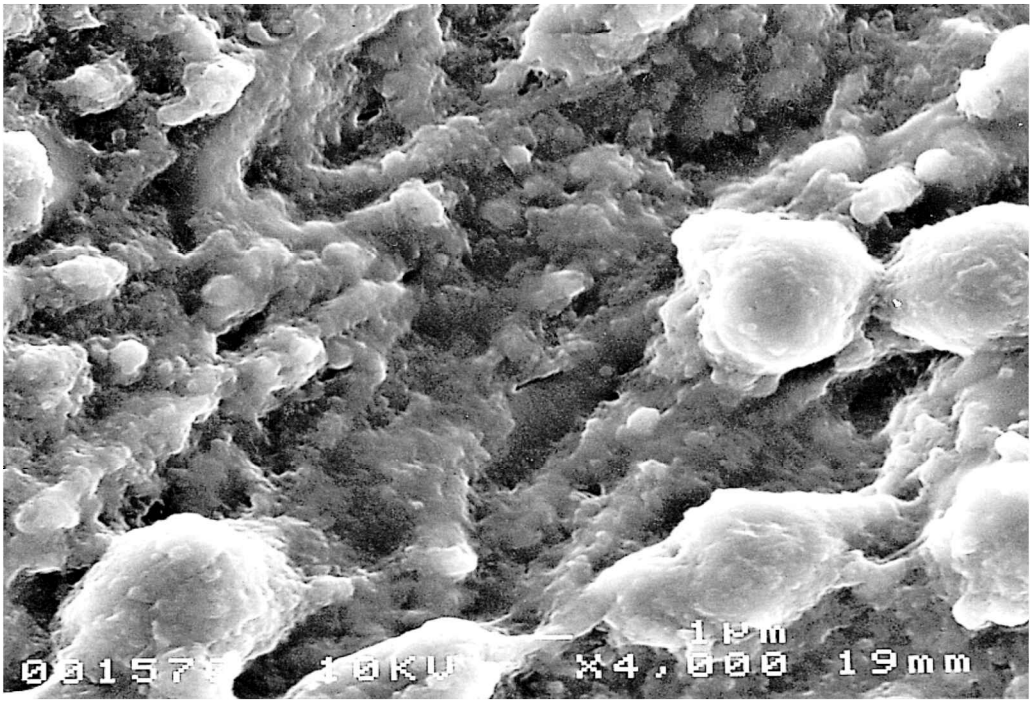

Figure 4 Biofilm present on the lumen of an endotracheal tube that had been retrieved from an ICU patient.

only reduced the risk for late-onset pneumonia, as the incidence of early-onset pneumonia was not statistically different. Driks et al (1987), in a study involving 130 patients, showed that using sucralfate as SUP could reduce the risk of VAP, as it maintains the natural gastric acid barrier. The authors studied the role of gastric colonisation and reported patients in the antacid or H_2-receptor antagonists group had a higher proportion of gastric aspirates with a pH > 4 and higher concentrations of Gram-negative bacteria in gastric aspirates, pharyngeal swabs and tracheal aspirates than those in the sucralfate group. The rate of pneumonia was twice as high, and Gram-negative bacteria were isolated more frequently from tracheal aspirates of patients with nosocomial pneumonia in the antacid or H_2-receptor antagonists group than in the sucralfate-treated group. Conversely, this finding does not enjoy universal acceptance and other groups have observed no statistical difference in the rate of pneumonia in patients receiving acid-neutralising agents versus sucralfate (Pickworth et al 1993; Thomason et al 1996; Cook et al 1998b). Thomason et al (1996) reported a trend toward decreased pneumonia in the sucralfate-treated group after study day four. Furthermore, Cook et al (1998b), in a large clinical trial with 1200 patients, stated that there was no significant difference in the rates of VAP between ranitidine- and sucralfate-treated patients, although the relative risk (1.18) suggested a trend toward a lower rate of pneumonia among patients receiving sucralfate, thus supporting the theory that sucralfate may have a protective, although limited, effect against pneumonia.

In related studies, involving 114 surgical patients (Hanisch et al 1998) and 167 patients with severe head injury (Metz et al 1993), respectively, there was no significant difference in VAP rates with those given ranitidine or placebo. Conversely, Apte et al (1992) reported that pneumonia developed significantly earlier in the ranitidine group, although fewer patients (32) were investigated and the patients who received ranitidine may also have received antacids. The administration of antacids, either

Table 2 The mechanism of action of the various pharmacological agents used in SUP[a].

	Sucralfate	Antacids	H_2-receptor antagonists
Gastric pH	0–(↑)	↑↑	0–↑↑
Pepsin secretion	↓	↓	0–↓
Bile acids	↓	↓	0
Prostaglandin (PG) release	↑	↑	0
Mucus secretion	↑ + PG independent	↑	↓
Bicarbonate secretion	↑ + PG independent	↑	0
Mucosal blood flow	↑	↑	0–↓
Cell renewal	↑ + PG independent	↑	0

[a]Amended from Tryba & Cook (1997). PG, prostaglandin; ↓↓, extensive decrease; ↓, decrease; ↑↑, extensive increase; ↑, increase; 0, no effect.

alone or in combination with H_2-blockers may lead to increased pneumonia rates, compared with H_2-blockers alone. This is due to greater acid neutralisation with antacids and a higher gastric volume with increased potential for aspiration.

The relative effects of sucralfate versus placebo on the incidence of VAP are unclear due to lack of data. Ben-Menachem et al (1994) showed an increased incidence of nosocomial pneumonia in those receiving sucralfate but the difference was not significant from the control group. A meta-analysis by Messori et al (2000), comparing the incidence of pneumonia with ranitidine and sucralfate, found a significantly increased risk of pneumonia with ranitidine. An earlier meta-analysis performed by Cook et al (1996) claimed that sucralfate is associated with lower rates of pneumonia and mortality, compared with H_2-blockers. This would suggest an overall trend to a lower incidence of VAP in comparison with agents that increase gastric pH. However, simply surmising that any intervention that increases gastric pH is inappropriate is not justified. The wide range in the occurrence of VAP may be explained by other factors that are not considered in many of the studies highlighted. Patients with a baseline gastric pH > 4 may benefit more if given sucralfate compared with a patient with pH < 4, as commonly occurs in the critically ill. Gastric volume, as well as pH, must be considered (antacids increase gastric volume as well as pH, as does continuous enteral feeding), as must the effects of the patient's position. However a recent trial (Cook et al 1998b) suggested that sucralfate may provide less efficient SUP than H_2-receptor antagonists, despite the latter agents' potential for increasing the risk of VAP. Reports that patients receiving ranitidine had a significantly lower risk of clinically important gastrointestinal bleeding than those treated with sucralfate (relative risk 0.44, 95% CI = 0.21–0.92) does not warrant the widespread use of sucralfate for SUP in the hope of preventing VAP. This was in contrast to results of a previous meta-analysis by Cook et al (1996) whereby sucralfate was deemed equivalent to H_2-receptor antagonists despite sparse data (based on four trials).

Antibiotics

Systemic

A high incidence of nosocomial infections in ICU patients is associated with high usage of antibiotics. Antibiotics represent one of the most frequently prescribed classes of drugs in hospitalised patients, with the total antibiotic usage in ICUs generally being ten times greater than in general hospital wards (Roder et al 1993). In a one-year prospective study (Bergmans et al 1997) the antibiotic use in a general ICU was recorded for 515 admissions by categorising the indications for antibiotic use into three groups – prophylaxis, bacteriological proven infection (BPI) therapy and therapy for non-BPI. This showed that 99% of all ICU-acquired infections occurred in intubated patients and as a result 90% and 95% of total antibiotic use and cost, respectively, were attributed to this group. The respiratory tract was the most significant site of infection, accounting for 43% of BPI and 67% of non-BPI. Thus, prevention of infection had the greatest potential to reduce overall antibiotic use.

The systemic use of antibiotics in patients who are postoperative, undergoing mechanical ventilation or are critically ill is utilised to prevent nosocomial pneumonia but the unreliable effectiveness of such regimens and subsequent increase in antibiotic resistance to infections poses problems. Yet there are situations where it is standard clinical practice to prescribe broad-spectrum parenteral antibiotics to aid the patient's recovery, such as febrile neutropenic patients undergoing mechanical ventilation (Pizzo 1990). Nevertheless, the use of parenteral broad-spectrum antibiotics to prevent nosocomial pneumonia is not advocated because of the increasing threat of superinfection (Louria et al 1962; Kollef 1993; Villers et al 1998).

Various measures to suppress the emergence of antibiotic resistance in nosocomial infections have been suggested (Goldman et al 1996) as exemplified by Kollef et al (1997b), who demonstrated that a scheduled change of the antibiotic class used for treatment of suspected infection reduced the incidence of nosocomial pneumonia caused by antimicrobial-resistant Gram-negative bacteria. Subsequently, Evans et al (1998) illustrated the benefit of a computer-assisted management program in improving the quality of patient care; which led to a significant reduction in antimicrobial susceptibility mismatches (12 vs 206, $P < 0.01$). ICU patients with pulmonary infiltrates, but not clinical infection, receiving empiric antibiotics, vary from 34 to 74% (Vincent et al 1995; Bergmans et al 1997; Singh et al 1998). Singh et al (2000) carried out a study in an attempt to resolve indiscriminate antibiotic prescribing in ICUs, when faced with uncertainty in accurately diagnosing pneumonia. Patients with a low likelihood of pneumonia were randomised to receive either standard therapy (choice and duration at the clinician's discretion) or a limited regimen of ciprofloxacin with review after three days. Antibiotics were continued for more than 3 days in the standard-therapy group – 90% (38/42) compared with 28% (11/39) in the limited-regimen group. Antimicrobial resistance developed in 35% and 15% in the standard- and limited-therapy group respectively. Mortality and length of ICU stay did not differ despite the lower cost and shorter duration of therapy in the limited-regimen group. Implications for this study are that prolonged antibiotic use in the standard-therapy group was unnecessary, inappropriate and may explain the differences in resistance between the two groups.

A recent investigation suggested that the administration of prophylactic parenteral antimicrobials to patients with coma might reduce the incidence of VAP. Sirvent et al (1997), in a novel study, used short-term prophylactic parenteral antibiotics in an attempt to prevent pulmonary infections in coma patients with head injuries and stroke that were undergoing mechanical ventilation. Fifty patients received intravenous cefuroxime (1500 mg 12-hourly after intubation for two doses) and fifty patients, not receiving cefuroxime, formed the control group. There was a significant difference in the incidence of pneumonia (24% of the treated patients and 50% of the controls) but

in the control group 17 patients had previously received prophylactic antibiotics. However, early-onset pneumonia was responsible for 67% and 72% of pneumonia cases in the treated and control group, respectively. This study, like others, demonstrated that neurological trauma patients (Korinek et al 1993) are susceptible to early-onset pneumonia, which accounted for 70% of all cases. The incidence of Gram-negative bacterial pneumonia did not differ between groups although there was a significant incidence of Gram-negative bacterial pneumonia in patients in the control group who had received previous antibiotic therapy. These patients may have received longer courses, as compared with the two doses in the treated group, but this information was not available. This agrees with published literature indicating an increase in VAP, caused by pathogens such as *P. aeruginosa* and *Actinobacter* spp, associated with previous antibiotic usage (Rello et al 1993; George 1995). The authors claimed that the use of cefuroxime or previous use of antibiotics (or both) in the control group before the pneumonia episode had a protective effect against its development and if the control group had not received any antibiotics the results probably could have been more significant. It seems a protective effect was observed in controls that had previously received prophylactic antibiotics, protecting against early-onset pneumonia, making them more susceptible to Gram-negative bacterial pneumonias than those control subjects who had not previously received antibiotics. The study suggested that there was no reason to give long-term antibiotics as a preventative measure against pneumonia, which may increase the cost and the emergence of resistant strains. No differences were found in mortality or morbidity between the two groups. The strategy here was simpler and more cost effective than selective decontamination of the digestive tract, as discussed later, with the reduction of nosocomial pneumonia due mainly to decrease in isolates of staphylococci, *Haemophilus*, and streptococci and therefore only useful for early-onset pneumonia.

A priority in preventing VAP, particularly antibiotic-resistant pneumonia, is restricting the nonessential use of antibiotics. The range of potential pathogens varies between ICUs, thus surveillance is needed to ensure robust antibiotic prescribing practices. Any resulting recommendations are based on data from individual centres and will have limited relevance to other sites, and in the main should only be implemented in the individual ICU. To date, in the absence of relevant data, the use of broad-spectrum parenteral antibiotics in preventing the occurrence of VAP is not advocated due to the increasing frequency of pneumonia caused by *P. aeruginosa* and *Acinetobacter* spp, which are associated with high mortality rates (Rello et al 1993; George 1995).

Selective decontamination of the digestive tract (SDD)

The use of SDD, a strategy to prevent nosocomial infection, has been based on the concept of colonisation resistance, first described in 1971 (Van der Waaij et al 1971), whereby intact, anaerobic intestinal flora has a protective effect against excessive growth of facultative aerobic bacteria. More specifically, SDD aims to eradicate enteric Gram-negative bacteria, *P. aeruginosa, S. aureus* and yeasts in the oropharynx, stomach and gut and to prevent further acquisition and secondary colonisation of such organisms while not affecting relatively harmless bacteria such as enterococci, *Staphylococcus epidermidis* and anaerobes. This method involves application of a non-absorbable antibiotic paste to the oral cavity and decontamination of the rest of the gastrointestinal tract by local administration of the same antibiotics. In addition, systemic antimicrobials are administered to prevent early endogenous infection, which may occur during the first days of intubation with the regimen of SDD. Regular cultures of throat swabs and faeces are taken to monitor the effectiveness of SDD and optimal hygiene is maintained to prevent cross infection. SDD was first used in 1980 to prevent bacterial infection in patients with granulocytopenia (Sleyfer et al 1980). This regimen was subsequently modified for use in preventing infection in mechanically ventilated trauma patients (Stoutenbeek et al 1984). A combination of non-absorbable antibiotics, including polymixin, tobramycin and amphotericin B, was applied in a paste (Orabase^{TM}) four times daily to the oropharynx and administered as a suspension four times daily, either orally or via nasogastric tube. Amphotericin is used to prevent yeast overgrowth, while polymixin and tobramycin cover for aerobic Gram-negative bacteria, *S. aureus* and *Ps. aeruginosa* and are non-absorbable. In adition, intravenous cefotaxime was administered for systemic prophylaxis against endogenous sources of infection, giving excellent cover against aerobic Gram-negative bacteria, limited cover against *S. aureus* and *S. pneumoniae* and minimal activity against anaerobes. This study reported that the incidence of respiratory-tract infections decreased from 59% (historical controls) to 8% in patients receiving SDD. This was a non-randomised, unblinded study with little detail given on patient characteristics. Regimens have since been altered to reduce cost and complexity (e.g., by substituting gentamicin or norfloxacin for tobramycin).

SDD has been studied extensively with approximately 50 randomised trials and six meta-analyses published (Table 3). Despite this extensive body of literature, there is continuing controversy over the rationale and use of SDD based on uncertainty regarding effectiveness, cost implications, appropriate antibiotic usage, patient selection and survival, and hospital settings where bacterial colonisation may be endemic. This uncertainty may stem from variation in the regimen used with different types of decontamination, for example decontamination of the oral cavity, intestine and systemic prophylaxis as opposed to the oral cavity only, thus making correlation of the studies difficult.

The majority of studies (Unertl et al 1987; Kerver et al 1988; Ulrich et al 1989; Rodriguez-Roldan et al 1990; Aerdts et al 1991; Blair et al 1991; Pugin et al 1991; Jacobs et al 1992; Rocha et al 1992; Winter et al 1992; Korinek et al 1993; Quinio et al 1996; AbeleHorn et al

Table 3 Results of six meta-analyses on SDD[a].

Reference	No. of trials	No. of patients	Study selection requirements	Outcome measure (95% CI) VAP	Mortality
Vandenbrouke-Grauls & Vandenbrouke (1991)	6	998	None	Odds ratios *0.21 (0.15–0.29)	Odds ratios *0.91 (0.67–1.23)
	6	491		#0.12 (0.08–0.19)	#0.70 (0.45–1.09)
SDD Trialists Group (1993)	22	4142	Prospective randomised	Odds ratio 0.37 (0.31–0.43)	Odds ratio 0.90 (0.79–1.04)
Heyland et al (1994)	25	3395	Prospective randomised	Relative risk 0.46 (0.39–0.56)	Relative risk 0.87 (0.79–0.97)
Kollef et al (1994)	16	2270	Prospective randomised or Double-blind cross-over	Risk difference 0.15 (0.12–0.17)	Risk difference 0.02 (−0.02–0.05)
D'Amico et al (1998)	16	3361	Prospective randomised with combined SDD	Odds ratio 0.35 (0.29–0.41)	Odds ratio 0.80 (0.69–0.93)
	17	2366	Prospective randomised with topical SDD	Odds ratio 0.56 (0.46–0.68)	Odds ratio 1.01 (0.84–1.22)
Nathans & Marshall (1999)	11	1207	Prospective randomised with >75% postop. or trauma patients	Odds ratio 0.19 (0.15–0.26)	Odds ratio 0.7 (0.52–0.93)
	10	1513	Prospective randomised with <25% postop. or trauma patients	Odds ratio 0.45 (0.33–0.62)	Odds ratio 0.91(0.71–1.18)

[a]Modified from Bonten et al (2000). SDD, selective decontamination of the digestive tract. *Historical control group; #randomised control group.

1997; Palomar et al 1997; Sanchez-Garcia et al 1998) indicate that SDD significantly reduced the incidence of VAP, while only a few investigators have reported a reduction in mortality (Rocha et al 1992). This has led to doubts about the usefulness of SDD as a preventative strategy for VAP.

Several factors may be postulated as reasons for such a discrepancy. The wide range in the incidence of VAP, in both control and study group, may be attributed to differences in how pneumonia was diagnosed. Specificity of diagnoses based on clinical, radiological and microbiological criteria is believed to be poor, with failure to differentiate between colonisation and infection. The use of bronchoscopic techniques is recommended in studies and when used, the incidence of VAP was reduced when compared with clinical, radiological and microbiological criteria (Pingleton et al 1992; Bonten et al 1997). Bergmans et al (2001) confirmed VAP diagnosis on positive quantitative cultures from bronchoscopic techniques with a reported incidence of 23% in the control group. This contrasts with the findings of Rodriguez-Roldan et al (1990) and Pugin et al (1991), who reported an incidence in the control group of 73% and 78%, respectively, when using clinical and microbiological criteria.

The patient group selected will also affect outcomes. A population of ICU trauma patients (Stoutenbeek et al 1984) will be different from a group of medical ICU patients who may have had previous antibiotic treatments, serious underlying disease and increased risk of colonisation with multi-drug resistant (MDR) bacteria (e.g. MRSA). Brun-Buisson et al (1989) and Gastinne et al (1992) found SDD to have little benefit on the incidence of VAP when they treated a medical ICU population using intestinal decontamination, and oropharyngeal and intestinal decontamination, respectively, versus controls.

Jacobs et al (1992) used low-dose dopamine for SUP in all patients and sucralfate in patients not receiving enteral nutrition or who had not been prescribed H_2-receptor antagonists. Of the control group, 53% and 16% received enteral nutrition and sucralfate, respectively, in comparison with the study group (31% received enteral nutrition and 33% received sucralfate). Sucralfate may reduce the incidence of VAP, whereas enteral nutrition is claimed to be a risk factor for VAP. This needs to be considered when looking at the results of a significantly reduced incidence of VAP in those who received SDD. This is in contrast to the work of Bergmans et al (2001), where more control patients received sucralfate and the study patients received more enteral feeds, favouring the control group (i.e. heightening beneficial effects of the oropharyngeal decontamination). Palomar et al (1997) administered H_2-receptor antagonists for SUP. As reported earlier, this may increase the incidence of VAP. Rodriguez-Roldan et al (1990) stated sucralfate or antacid plus ranitidine was given for SUP according to a randomised open protocol, but no further mention was made of who received which regimen. Also, in this study chlorhexidine was applied to the oral cavity in both groups every 6 h as a local disinfectant. This may have had an effect on the outcome of this small study, with a relative risk reduction of 1 for VAP. With regards to the severity of illness, Blair et al (1991) noted the greatest reduction in nosocomial infection in patients with mid-range APACHE II scores.

It is evident that there are no studies to compare varying dosages of antibiotic agents and therefore it is not possible, on the basis of the available studies, to determine

the optimal combination or concentration of antibiotics to be used as part of an SDD regimen.

Studies using only oropharyngeal and intestinal decontamination versus controls (Unertl et al 1987; Korinek et al 1993; Quinio et al 1996) showed a significant reduction in the incidence of pneumonia but not in mortality. Gastinne et al (1992) and Wiener et al (1995) demonstrated that oropharyngeal and intestinal decontamination had no impact on the incidence of VAP, although colonisation with MDR bacteria was endemic in these sites, which may explain their results. This was also the case in the ICUs, where authors of several studies (Hammond et al 1992; Ferrer et al 1994; Lingnau et al 1997) concluded that SDD (oropharyngeal and intestinal decontamination, with systemic antimicrobial prophylaxis), versus systemic antimicrobial prophylaxis alone, had little positive effect on pneumonia rates, although, in this situation, it may be argued that systemic prophylaxis alone had a protective effect against the development of VAP, and not the topical application of antibiotics. However, SDD should not be used in an ICU where there is endemic colonisation with drug-resistant bacteria. Brun-Buisson et al (1989) found that overgrowth of staphylococci and enterococci occurred more often in SDD-treated patients than in control patients, while Hammond et al (1992) reported an increased emergence of infections with *Acinetobacter* spp. following the use of SDD.

Chlorhexidine was shown to reduce the incidence of respiratory nosocomial infections when used in a cardiovascular ICU (DeRiso et al 1996). Chlorhexidine gluconate oral rinse was used twice daily in the double-blind placebo-controlled trial involving 353 patients. This type of oropharyngeal decontamination is clearly a less expensive and labour-intensive regimen than those previously described. However, further appraisal needs to be undertaken before any recommendations for its use can be made.

To date, the cost-benefit of SDD has not been accurately assessed. While many studies calculate the acquisition cost of antibiotic regimens, few take into account the cost of surveillance cultures. AbeleHorn et al (1997) calculated that the average daily antibiotic cost per patient was significantly lower in the study group and total antibiotic cost per treated patient was lower. This study used only selected oropharyngeal decontamination and systemic prophylaxis, whereas SDD is much more expensive. The study of Quinio et al (1996) was the only other to show that total antibiotic cost was lower in the treatment group (oropharyngeal and intestinal decontamination). Many investigators make no reference to overall antibiotic use in the ICU (Brun-Buisson et al 1989; Rodriguez-Roldan et al 1990; Pugin et al 1991; Jacobs et al 1992; Ferrer et al 1994). When van Nieuwenhoven et al (2001) investigated the relationship between the effect of SDD on pneumonia and mortality, and methodological trial quality, they highlighted an inverse relationship between the quality of the studies and reported benefits (incidence of nosocomial pneumonia) for those receiving SDD. They also found a small but significant reduction in mortality when analysing studies deemed to be high quality.

Earlier meta-analysis highlighted the discrepancy between patient mortality and rates of pneumonia, although one meta-analysis (Selective Decontamination of the Digestive Tract Trialists Collaboration Group 1993) showed a modest reduction in mortality when systemic antibiotics were used. However, two recent meta-analyses showed a significant reduction in mortality (20% and 30%) in a mixed population of surgical and medical patients, and in surgical patients, respectively, where the combination of topical and systemic prophylaxis had been investigated (D'Amico et al 1998; Nathens & Marshall 1999). This led to claims (Van Saene & Baines 1999) that SDD had positive results on patient care and was an evidence-based intervention. However, when patients receiving total decontamination (topical and systemic antimicrobial prophylaxis) were compared with control patients who received no prophylaxis, there was a reduction in mortality. This was in contrast to the outcome when total decontamination was compared with systemic prophylaxis, or when topical prophylaxis was compared with no prophylaxis. The majority of patients with improved survival (D'Amico et al 1998) were surgical and trauma patients. It was argued (Van Saene & Baines 1999) that systemic antibiotic prophylaxis alone may be responsible for the reduction in mortality and, in fact, advocate the use of prophylactic parenteral antimicrobials in such patient groups.

Concerns about the unpalatibility, administration difficulty, increased nursing time and costs and development of antimicrobial resistance and infection with Gram-negative bacteria and other drug-resistant pathogens have not encouraged the routine use of SDD in the critically ill. It is clear that for SDD certain populations may benefit: surgical rather than medical patients and those who are immunosuppressed or are undergoing liver transplant and oesophagectomy (Vincent 1999). Gorman et al (1993) and Adair et al (1993) demonstrated that SDD did not have any effect on reducing VAP-causing pathogens. Several investigators have shown an increase in the rates of isolation of Gram-positive bacteria when SDD is used (Gastinne et al 1992; Hammond et al 1992; Rocha et al 1992). Cockerill et al (1992) demonstrated the increased incidence of gentamicin-resistant enterococci and Hammond et al (1992) showed an increase in MRSA colonisation, while Blair et al (1991) reported tobramycin-resistant aerobic Gram-negative bacteria in those treated with SDD. Although overt infection with MDR bacteria has not been reported, this does not mean that the use of SDD, if applied on a larger scale, would not lead eventually to the emergence of resistance. Unfortunately, in light of the short duration of SDD regimens, there is insufficient information about the long-term microbiological effect, whereas early studies using long-term tracheal instillation of antibiotics have reported the emergence of MDR bacteria (Feeley et al 1975). To demonstrate a significant reduction in mortality, larger number of patients would have to be investigated than has been the case to date.

The routine use of SDD as a measure of infection prevention in the ICU remains controversial and has not found favour in North America (Kollef 1999). The lack of

clarity regarding the effects on survival, duration of mechanical ventilation, cost and possible selection of multiple drug resistant pathogens means that any advantages of SDD may well be outweighed by potential disadvantages. A sufficiently large prospective randomised double-blind study may resolve the quandary of the positive benefits of SDD in the ICU.

Aerosolised antibiotics

The administration of parenteral or oral antibiotic should achieve a high drug concentration to maximise its killing effect at the infection site. Yet commonly with such routes of administration, sub-optimal levels of antimicrobials are reached at the various infection sites compared with the circulatory drug concentrations. In such cases, unacceptably high doses of antibiotic would have to be prescribed to achieve the necessary drug concentrations. Antimicrobial distribution may be hampered due to the patient's anatomic composition and the agent's physiochemical characteristics (Flume & Klepser 2002). However, drug delivery directly to the lung by nebulisation allows higher concentrations into the lung and may minimise systemic toxicity. Aerosol drug delivery has evolved extensively in the last 50 years and is largely based on antibiotics used in cystic fibrosis (CF). Figures 5 and 6 contrast the results from studies illustrating the different routes of administration of the aminoglycoside tobramycin.

With antibiotic nebulisation, sputum concentrations were much higher than achieved by intravenous administration, while there is negligible systemic absorption of the drug. Compared with intravenous administration, nebulised administration allows a greater amount of drug to be delivered to the lung without the risk of nephrotoxicity and ototoxicity (Morgan et al 1999). Mendelman et al (1985) showed that ten times the minimum inhibitory concentration (MIC) of tobramycin was needed to suppress the growth of *Ps. aeruginosa* in the sputum of CF sufferers and a 25-fold excess is required for a bactericidal effect. This is pertinent to VAP whereby infection with *Ps. aeruginosa* is of concern, especially in late-onset pneumonia (Fagon et al 1993).

With regard to prevention of pneumonia, Klastersky et al (1974) carried out a small clinical trial with endotracheally administered gentamicin in tracheostomy patients. This method showed initial promise but was hampered by poor distribution throughout the lung. Klick et al (1975), using aerosolised polymixin directly into the oropharynx, decreased upper-airway Gram-negative colonisation in ICU patients. When used continually, rather than intermittently, oropharyngeal antibiotics were associated with an increased incidence of pneumonia with resistant bacteria and this regimen was abandoned (Feeley et al 1975). Palmer et al (1998) demonstrated that nebulised antibiotics can be effectively delivered to patients receiving mechanical ventilation, with measurable changes in clinical and airway inflammatory indicators (decreased levels of inflammatory cells and mediators), significant reduction in sputum volume, and eradication of *P. aeruginosa* and other Gram-negative pathogens in most cases. The study involved only six patients who received nine courses of either nebulised gentamicin or amikacin for 14–21 days. Serum aminoglycoside was undetectable in all patients, except for one who was in renal failure. All patients were ventilator dependent and all were medically stable. As stated by the authors, this study was not a clinical trial but a quantitative assessment.

A preliminary double-blind placebo-controlled study with 38 mechanically ventilated patients with VAP was carried out in France (Le Conte et al 2000), assessing renal and respiratory tolerance of nebulised tobramycin. The authors concluded that aerosolised tobramycin was well tolerated in patients with documented nosocomial pneumonia. Extubation by day 10 was achieved in 35% of

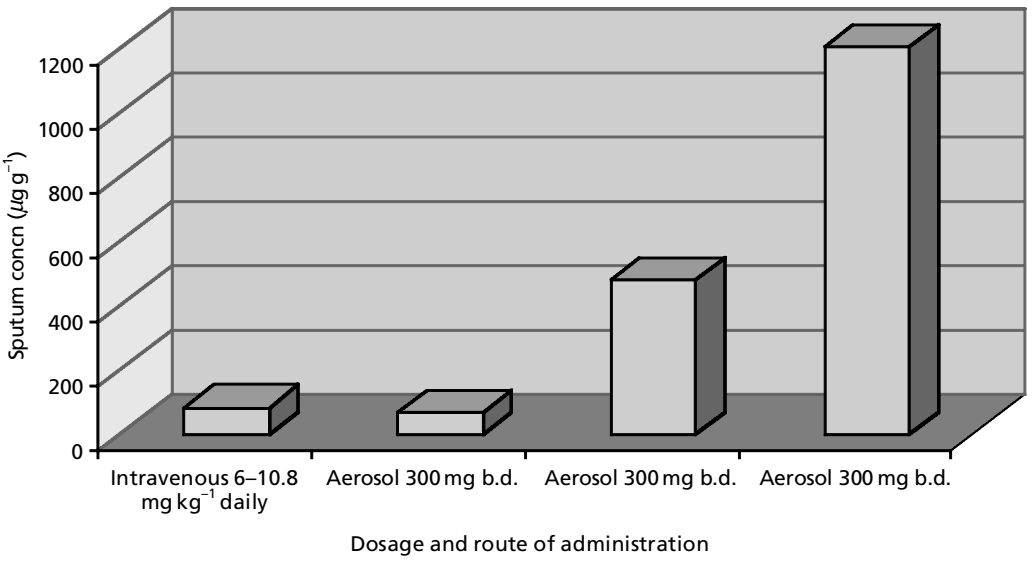

Figure 5 Sputum concentrations of tobramycin (Mendelman et al 1985; Eisenberg et al 1997; Ramsey et al 1997).

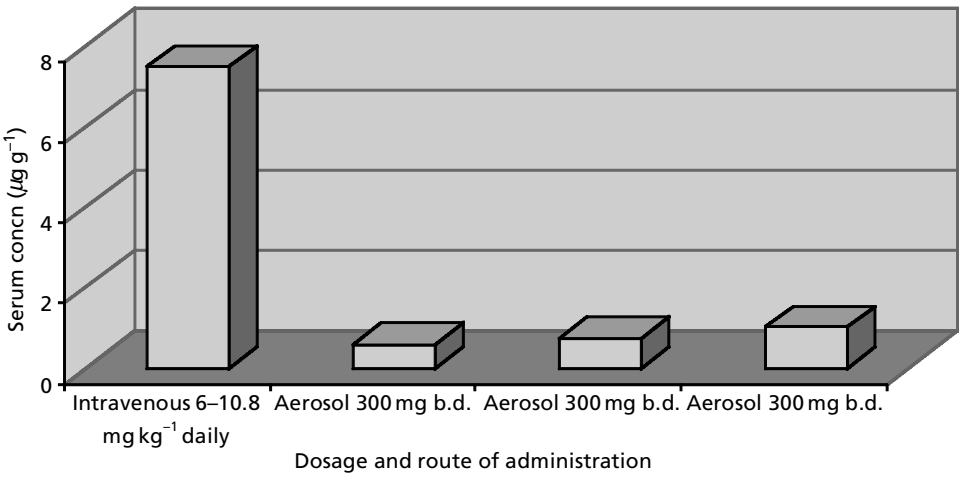

Figure 6 Serum concentrations of tobramycin (Mendelman et al 1985; Eisenberg et al 1997; Ramsey et al 1997).

patients who received nebulised tobramycin and in 18.5% of the placebo group but the difference was not statistically significant. Little information was given on patient characteristics and both groups received intravenous tobramycin with a beta-lactam antibiotic. Adair et al (2002), in a study involving 36 patients (12 received nebulised gentamicin 8 mg every 8 h, 12 received intravenous cefotaxime 1 g every 12 h and 12 received intravenous cefuroxime 750 mg every 8 h), demonstrated that nebulised gentamicin was more effective in preventing the formation of biofilm in the endotracheal lumen than either intravenous cefotaxime or cefuroxime in high-risk ventilated patients. Prophylaxis was continued for the duration of intubation. The results suggest that the regimen has a role in reducing the incidence of VAP although further investigations are required. It was noted that over the study duration there was no increase in the rate of Gram-negative bacterial resistance. Previously, Gorman et al (1993) showed that, unlike nebulised antibiotics, SDD was not successful in preventing biofilm formation or in eradicating established biofilm.

The use of nebulised antibiotics in VAP allows attainment of higher pulmonary drug concentrations than parenteral administration of antimicrobials and, compared with SDD, may be less expensive and easier to administer. Other potential benefits may include reduced morbidity and exposure to systemic antimicrobials and improved survival rates.

Advances in biomaterial design and function

The increased resistance of bacterial biofilms to antimicrobial agents and the inaccessibility of the bacterial biofilm to antibiotics following conventional (oral or parenteral) administration have ensured that the treatment of VAP is an extremely difficult challenge (Gorman et al 2001). The limited success of many of the current regimes to treat this clinical condition has directed scientific strategies that involve modification of the design and function of biomaterials to ensure that a greater resistance to microbial colonisation occurs. Central to this philosophy is the use of biomaterials as a matrix for the controlled delivery of antimicrobial agents and the use of novel microbial anti-adherent coatings (Gorman & Jones 2003). The problem of medical-device-related infection is common to all medical devices (Tunney et al 1996; Gorman & Jones 2003) and, accordingly, the above strategies have been employed for the prevention of infection of other classes of medical devices (e.g., ureteral stents, urethral catheters, central venous catheters). However, despite the emergence of a growing body of literature on this topic, there has been a relatively limited application of the above technologies to the resolution of ventilator-associated pneumonia. Therefore, the following will serve to illustrate some of the approaches that may be employed in this clinical condition.

The incorporation of therapeutic agents within polymeric biomaterials has been employed to offer controlled release of the chosen agent to the surrounding fluids or tissues for several decades (Chien 1992). However, it is only within the last decade that a conscientious effort has been made to utilise this strategy for the prevention of medical-device-related infection. In this approach, the antimicrobial agent is released at a controlled rate directly to the microbial biofilm and the fluid that surrounds the implanted medical device. Importantly, bactericidal concentrations of the antimicrobial agent may be achieved and maintained within the microbial biofilm for a prolonged period, preferably for the duration of implantation of the device. The simplest method that has been employed for the incorporation of antimicrobial agents within medical devices involves immersion of the device in a solution of the desired antimicrobial agent. However, the clinical success of this approach has been varied due primarily to the poor adsorption or absorption properties of the drug onto or within the polymer, the inability of the polymer to swell in the chosen solvent, the poor solubility

of certain antimicrobial agents in aqueous solutions and, finally, the rapid desorption characteristics of the antimicrobial agent from the polymer following contact with a biological fluid (Gorman & Jones 2003). Using an animal model, GoeauBrissonniere et al (1999) described reduced adherence of Gram-positive (*S. aureus* and *S. epidermidis*) and Gram-negative (*E. coli*) bacteria following immersion of different materials (silicone, silver-coated stents and hydrogel-coated stents) in a rifampicin solution when compared with systemic antibiotics. Similarly, Reid et al (1994) described reduced adherence of *P. aeruginosa* to silicone-based catheters that had previously been soaked in solutions of ciprofloxacin. However, not all reports have been positive in this regard, with Cormio et al (1997) concluding that the pre-treatment of silicone and other ureteral stent biomaterials with tobramycin did not affect the subsequent bacterial adherence. Therefore, these studies have served to highlight that careful consideration of the chemistry of both the therapeutic agent and biomaterial is required to ensure that sufficient adsorption or absorption of the therapeutic agent from solution onto the biomaterial occurs. As endotracheal tubes are made primarily of either polyvinylchloride or silicone, the adsorption or absorption of antimicrobial agents from aqueous solution would be expected to be relatively low unless the drug possesses surface-active properties, which would facilitate drug adsorption. Under these circumstances, one method that may be useful to enhance the uptake of antimicrobial agent is to employ a biocompatible solvent with a greater affinity for the biomaterial but that does not facilitate dissolution of the polymer. Following evaporation of the solvent, a greater mass of antimicrobial agent may be absorbed into the biomaterial. This strategy has been employed by Becket et al (1997) and Kohnen et al (1998). One point that should be considered concerning the immersion method (independent of the choice of solvent) is the relatively long period of immersion that may be required to obtain maximum drug uptake, which may in turn further limit the utility of this approach.

To enhance the performance of biomaterials, alternative strategies have involved coating medical devices with antimicrobial agents, as this approach will allow greater control over the subsequent release of antimicrobial agents. Using this technology, several combinations of antimicrobial agents have been shown to be effective. For example, polyurethane vascular catheters have been coated with minocycline and ethylenediaminetetra-acetate and have been shown to reduce bacterial colonisation both in-vitro and in-vivo (Raad et al 1997a). Similarly, Raad et al (1997b) reported that catheters that had been coated with minocycline and rifampicin reduced the incidence of catheter-related infection. Other antimicrobial agents that have been coated onto medical devices (and have exhibited varying degrees of laboratory and clinical success) include silver sulfadiazine–chlorhexidine (Darouiche et al 1999), chlorhexidine (Maki et al 1997), teicoplanin (Bach et al 1996) and silver (Gabriel et al 1996; Stickler et al 1996). Interestingly, there have been some reports of the lack of clinical efficacy of antibiotic-coated biomaterials. Pemberton et al (1996) reported that the incidences of catheter-associated bacteraemia with an uncoated catheter and a chlorhexidine–silver sulfadiazine catheter were similar, whereas Sheretz et al (1997) reported the incidence of catheter-related sepsis associated with an uncoated polyurethane catheter and a catheter coated with silver sulfadiazine–chlorhexidine differed. This disparity raises a number of problems associated with the use of an antibiotic-coated system that have not been adequately addressed. These include the nature and duration of the release of antibiotics, the initial mass of antibiotics in the coating and the compatibility of the antibiotics with the coating matrix. Unfortunately, the choice of polymeric matrix and antibiotic for the coating layer is performed independently and, as a result, the performance of the medical device is compromised. Nevertheless, the potential utility of this approach for the prevention of medical-device-related infection should not be overlooked and, indeed, this approach may be useful for the prevention of VAP.

One method by which the mass of antimicrobial agent within the medical device may be increased involves direct incorporation into the polymeric matrix, the greater available mass of polymer facilitating this process. This step may be accomplished by either polymerising the required monomers in the presence of the antimicrobial agent (e.g. hydrogels) or, alternatively, the antimicrobial agent may be processed (e.g. by injection moulding, extrusion) with the polymer during the manufacture of the medical device (Gorman & Jones 2003). Increasing the mass of antimicrobial agent incorporated within the medical device has two direct advantages, namely greater control of both the rate and duration of drug release that may be achieved when compared with either antimicrobial-coated systems or systems that have been produced by immersion of the device within a solution of antimicrobial agent. There have been several successful reports of the laboratory and clinical performance of these systems and, of direct importance to VAP, many of these reports have employed silicone and polyvinylchloride (biomaterials from which endotracheal tubes are manufactured). For example, Whalen et al (1997) incorporated chlorhexidine into silicone and reported that chlorhexidine was released in a controlled fashion for four weeks and that the antimicrobial-impregnated biomaterial possessed significant inhibitory activity against several microorganisms. Similarly, Schierholz et al (1994) described the manufacture, controlled-drug-release properties and biocidal activity of rifampicin-impregnated silicone. Jones et al (1996) described the reduced adherence of *Pseudomones fluorescens* to polyvinylchloride that had been impregnated with antimicrobial agents and, in particular, illustrated that the anti-adherent effect increased as a function of the concentration of incorporated antimicrobial agent. More recently, Jones et al (2002) examined the physicochemical and antimicrobial properties of hexetidine-impregnated (heat-cured) polyvinylchloride, designed as a novel endotracheal tube biomaterial. The authors illustrated that the release rate of drug may be manipulated by alteration of the mass of incorporated hexetidine and that there was a marked reduction in bacterial adherence (*S. aureus* and *P. aeruginosa*)

to the drug-loaded materials. However, of direct concern to the application of these biomaterials as endotracheal tubes was the deleterious effect of incorporated drug on the resultant mechanical properties. Remembering that the endotracheal tube is designed to offer patency of air flow, it is important that chemical (drug) additions to the polymeric matrix do not unduly affect the process of mechanical ventilation. Despite this, the authors concluded that polyvinylchloride containing up to 5% w/w hexetidine exhibited promise as endotracheal-tube biomaterial.

One final point that should be addressed concerning the clinical performance of antibiotic-impregnated polymers for use as endotracheal-tube biomaterials concerns the subsequent release of antibiotic within the respiratory environment. To date, all the clinical studies have been performed using biomaterials that have been inserted within aqueous environments (e.g., the circulatory system, the urinary system). Under these circumstances, the flow of a large volume of biological fluids adjacent to the surface of the medical device will facilitate drug release, allowing the drug at the surface of the device to partition into the fluids. If the antimicrobial-impregnated medical device is a granular matrix (i.e. the drug is dispersed within the polymer matrix) and drug release occurs as a result of pore formation within the polymer, aqueous fluid is required to facilitate drug release (Chien 1992). Unfortunately, the environment into which the endotracheal tube is placed is primarily hydrophobic in nature (due to the gaseous flow) and has limited access to aqueous fluids. Thus, in this scenario, the release of drugs from granular matrices will be severely compromised, and this will have serious consequences for clinical efficacy. This problem may be minimised by the selection of antimicrobial agents that possess good solubility in the parent polymer. Therefore, depending on the mass of antimicrobial agent present, a saturated solution of therapeutic agent within the polymer will be achieved and, accordingly, there will be a uniform molecular distribution of drug throughout the polymer matrix. Following bacterial attachment, the antimicrobial agent will be available to diffuse into the bacterial cell and produce a bacteriostatic or bactericidal effect. This approach requires careful consideration of the physicochemical properties of both the polymer matrix and the antimicrobial agent and has been described by Jones et al (2002). In this study, hexetidine was chosen as the antimicrobial agent due, in part, to its lipophilic properties and hence good solubility in endotracheal-tube polyvinylchloride. As described earlier, this novel biomaterial exhibited good bacterial anti-adherent properties and may therefore be a useful candidate for clinical evaluation. One further strategy that was described by the same authors, and which may be of interest to the design of endotracheal tubes, involves the use of novel surfactant bacterial anti-adherent coatings (Jones et al 2003). In this, the authors described the prolonged antibacterial (anti-*S. aureus* and -*P. aeruginosa*) properties of lecithin and lecithin–cholesterol coatings that were dip-coated onto endotracheal-tube polyvinylchloride. Based on in-vitro studies, it was concluded that these novel coatings may reduce the incidence of ventilator-associated pneumonia when employed as coatings on the lumen of endotracheal tubes. However, as is the case for many of the newer biomaterials and coatings, clinical evaluation is required to validate the initial promise.

Conclusion

There is controversy regarding the part played by gastric pH in the development of VAP but it is still widely believed that bacterial colonisation of the stomach, facilitated by antacids and H_2-blockers, is an important source of pathogens for VAP. Debate continues about the effectiveness of sucralfate in reducing the incidence of VAP as highlighted by several meta-analyses of the literature (Cook et al 1991b, 1996; Tryba 1991; Messori et al 2000). There is no definitive evidence that the risk of VAP is lower or that sufficient SUP is provided with sucralfate than H_2-blockers (Cook et al 1998b), but, as demonstrated by Prod'hom et al (1994) and Thomason et al (1996), sucralfate exerts a possible protective effect, significantly reducing the incidence of late-onset pneumonia. However, the widespread use of sucralfate in the hope of preventing VAP is not warranted.

Several studies have shown a protective effect of antibiotics among high-risk ICU patients (George et al 1998; Rello et al 1999). Sirvent et al (1997) demonstrated that short-term monotherapy prophylaxis might have a role in preventing VAP in ICU neurological trauma patients. Further investigation is required to determine the general applicability and safety of broad-spectrum parenteral antibiotic therapy for prevention of VAP. The use of broad-spectrum parenteral antibiotics for the prevention of VAP is not recommended, as widespread and prolonged use of prophylactic antibiotics may lead to the attainment of potentially resistant pathogens such as *Ps. aeruginosa* and *Acinetobacter* spp.

The routine use of SDD as a measure of infection prevention in the ICU remains controversial. Unfortunately, the short duration of SDD regimens means that there is insufficient data regarding their long-term microbiological effects, unlike early studies using long-term tracheal instillation of antibiotics, which reported the emergence of MDR bacteria (Feeley et al 1975). To demonstrate a significant reduction in mortality, a larger number of patients would have to be investigated than has been the case to date. Beneficial effects on outcomes such as duration of mechanical ventilation, ICU stay and amount of antibiotic use remain unproven, whereas selection of antibiotic-resistant pathogens remains a cause for concern. Thus the potential disadvantages of SDD may outweigh the advantages.

Earlier studies (Feeley et al 1975), due to lack of efficacy and subsequent emergence of resistance, discredited the use of aerosolised antibiotics. Despite this, the rationale for the use of nebulised antibiotics is that it may allow earlier extubation, reduce length of stay in ICU and possibly reduce mortality in patients undergoing mechanical ventilation. This area needs to be explored further, with

more investigations to determine the role of prophylactic nebulised antibiotics in the management of VAP.

The routine use of antibiotics in any form (oral, parenteral, topical or aerosol) may lead to selection of bacteria that are resistant to various antibiotics and subsequent difficult-to-treat infections. It is therefore vital that each ICU should have a local epidemiological surveillance programme to improve the efficacy of such regimens and positive mortality outcomes.

Finally, advances in biomaterial design and function offer exciting potential options for reducing the incidence of VAP. Of particular interest in this respect are biomaterials that possess an antimicrobial coating or those in which the antimicrobial agent is directly incorporated into the polymer matrix. The efficiency of the delivery of the antimicrobial agent to the microbial biofilm of these systems will be markedly greater than for conventional routes of antibiotic administration. However, while there have been several clinical evaluations of these systems following insertion within a range of body fluids (e.g. the circulatory system, the urinary tract), clinical evaluation of the efficacy of these systems within the respiratory tract, a site in which there is extremely limited contact of the device with aqueous fluids, has not been performed. Therefore, the suitability of these novel antimicrobial biomaterials for usage as endotracheal-tube materials requires urgent attention.

In conclusion, no prophylactic antibiotic strategy (including antimicrobial biomaterials) should be widely used until the implications for patients undergoing mechanical ventilation (colonisation with resistant bacteria, effects on morbidity and mortality, hospital costs) have been fully explored. However, there are encouraging strategies that offer preliminary promise for reducing VAP. It is recommended that the efficacy of these systems should be fully (and urgently) evaluated.

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