Chapter 15

Intensive Care Unit

Hakan Hanberger[1], Dominique L. Monnet[2], and Lennart E. Nilsson[3]
[1]Division of Infectious Diseases, Department of Molecular and Clinical Medicine, University Hospital, S-581 85 Linköping, Sweden; [2]Antimicrobial Resistance Surveillance Unit, National Center for Antimicrobials and Infection Control, Statens Serum Institut Denmark; [3]Division of Clinical Microbiology, Department of Molecular and Clinical Medicine, University Hospital, S-581 85 Linköping, Sweden

1. INTRODUCTION

Critically ill-patients admitted to intensive care units (ICUs) are highly susceptible to infections because of predisposing illnesses and the use of invasive procedures, and are therefore exposed to high antibiotic pressure. Use of antibiotics in the ICU must follow best clinical practice if the emergence of resistance to antibiotics is to be minimised. Antibiotic resistance is an important factor governing treatment success and mortality (Carmeli *et al*., 2002; Kollef and Ward, 1998; Kollef *et al*., 1999). The problem of resistance is greater in ICUs than in other hospital wards or primary care centres (Archibald *et al*., 1997; Hanberger and Nilsson, 2000; Hanberger *et al*., 2001a). Control of antibiotic resistance, that is, detecting, monitoring, and fighting the emergence of resistant bacteria is, therefore, especially important in the intensive care environment. According to a recent review of European ICUs, the prevalence of antibiotic resistance in bacteria was, with some exceptions, highest in ICUs in Southern European countries and in Russia, and lowest in Scandinavia (Hanberger *et al*., 2001a). This was also true for the key organism methicillin-resistant *Staphylococcus aureus* (MRSA) (Regnier, 1996; Vincent *et al*., 1995). Antimicrobial resistance also varies markedly by region and ward level in the United States, Canada, and Latin America with the highest resistance rates

Antibiotic Policies: Theory and Practice. Edited by Gould and van der Meer
Kluwer Academic / Plenum Publishers, New York, 2005

being found in Latin America (Burwen *et al*., 1994; Diekema *et al*., 1997; Edmond *et al*., 1999). As patterns of resistance change, physicians need to reassess standard therapies to ensure appropriate antibiotic coverage.

2. ANTIBIOTIC CONSUMPTION IN ICUs

Because data on antimicrobial use are reported using various measurement units, comparisons are only possible among ICUs using the same measurement unit. Several studies have reported antibiotic use expressed as a number of WHO Defined Daily Doses (DDD) per 1,000 patient-days in individual or groups of European ICUs. Depending on the ICU, antibiotic use ranged from 490 to 3,456 DDD per 1,000 patient-days (Erlandsson *et al*., 1999; Gruson *et al*., 2000; Hanberger *et al*., 2004; Kiivet *et al*., 1998; Lemmen *et al*., 2000; Naaber *et al*., 2000; Petersen *et al*., 1999; Vlahovic-Palcevski *et al*., 2000; Walther *et al*., 2002).

In one study, Bergmans *et al*. (1997) used the prescribed daily dose (PDD) as the measurement unit and reported 921 PDD per 1,000 patient-days in two Dutch general ICUs in 1994. The ICARE DDDs developed to report antibiotic use in Centers for Disease Control and Prevention (CDC) Project ICARE represent a form of PDDs (Capellà, 1993). In 40 US hospitals, which participated in Project ICARE during the period 1996–7, antibiotic use ranged from 413 to 927 ICARE DDD per 1,000 patient-days depending on the type of ICU (ICARE Surveillance Report, 1999). It is important to note that this does not correspond to total antibiotic use since Project ICARE did not collect data on all antibiotic classes used in these ICUs.

Other studies have collected data at patient level and expressed antibiotic use as the number of daily antibiotic treatments (all individual antibiotics received on a single day are taken into account) per 1,000 patient-days. In a group of four Danish ICUs, Petersen *et al*. (1999) reported that antimicrobial use ranged from 1,390 to 2,510 daily antimicrobial treatments per 1,000 patient-days. Although the highest use was reported from one ICU that routinely used selective decontamination of the digestive tract (SDD), antimicrobial use in this ICU is likely to have been underestimated because multiple agents for the SDD protocol were recorded as one single antimicrobial.

In the European Strategy for Antibiotic Prophylaxis (ESAP) study, the median antimicrobial use (including antifungals) was 928 daily treatments per 1,000 patient-days (range: 355–1,686) in 21 ICUs that did not use SDD (Monnet *et al*., 2000). In comparison, two ICUs that routinely used SDD reported 3,753 and 4,794 daily antimicrobial treatments per 1,000 patient-days and two other ICUs that used SDD for very selected indications only reported 997 and 1,085

daily antimicrobial treatments per 1,000 patient-days (Monnet *et al*., 2000). It seems that, when routinely used, SDD may represent the largest part of overall antimicrobial use in an ICU.

Data collected at patient level also allow the expression of antibiotic use in terms of exposure, either as a number of antibiotic exposure-days (several antibiotics received by a single patient on a single day count for one day of exposure) per 1,000 patient-days or as a percentage of ICU patients who received at least one antibiotic. Fischer *et al*. (2000) reported 546 antibiotic exposure-days per 1,000 patient-days in a Swiss paediatric ICU in 1998–9. The European Prevalence of Infection in Intensive Care (EPIC) one-day multicentre prevalence study performed in 1992 found that 62% of patients in 1,047 ICUs from 17 European countries received antibiotics (Vincent *et al*., 1995). A German point prevalence survey in 1994 found that 53% of ICU patients in 72 hospitals received antibiotics (Gastmeier *et al*., 2000). In a 3-month incidence study performed in 49 Spanish ICUs in 1996, 53% of patients received antibiotics (GTEI-SEMIUC, 1996). In the 21 ESAP ICUs that did not use SDD, a median 75% of patients received antimicrobials (range: 23–100%) (ESAP, unpublished data). Similar figures were found in a 2-week prevalence study carried out in 2000 in 23 Swedish ICUs (Hanberger *et al*., 2001b). Studies performed in individual adult ICUs reported that 68–80% of patients received antibiotics (Bourdain *et al*., 1999; Kollef *et al*., 2000; Røder *et al*., 1993; Tarp and Møller, 1997). In neonatal ICUs, studies performed in individual units showed that 24–46% of patients received antibiotics (Andersen and Meberg, 1999; Borderon *et al*., 1992; Fonseca *et al*., 1994; Tullus *et al*., 1988). However, much higher percentages were reported in selected groups of neonates. For example, the percentage of neonates receiving antibiotics was 92% in premature infants weighing less than 1,500 g at birth (Fonseca *et al*., 1994) and virtually 100% in preterm neonates (<30 weeks) requiring mechanical ventilation (Gortner, 1993).

Some studies have attempted to compare antibiotic use in ICUs and other hospital wards. In Project ICARE, the median rate of antibiotic use was higher in adult ICUs than in non-ICU areas combined (Fridkin *et al*., 1999). This was especially true for third-generation cephalosporins, intravenous vancomycin, penicillins with anti-pseudomonal activity, and intravenous fluoroquinolones. In three European hospitals, Kiivet *et al*. (1998) reported that antibiotic use expressed as a number of DDD per 1,000 patient-days was 2–6 times higher in ICUs than in surgical and medical units. In one US hospital, the total number of days of antibiotic therapy and total number of grams of antibiotic per patient-day were 1.5 times greater in the ICU than in non-ICU areas (White *et al*., 2000). In one Danish hospital, Tarp and Møller (1997), reported that 69% of patients in ICU received antibiotics as compared to only 24% and 17% in surgical and medical wards, respectively. Finally, antibiotic pressure in ICUs

is much higher than in primary care. In European Member States, antibiotic use in primary care in 1997 ranged from 8.9 DDD per 1,000 inhabitant-days in the Netherlands to 36.5 DDD per 1,000 inhabitant-days in France (Cars *et al*., 2001). Similar data from outpatients can be compared to antibiotic use in hospitals (including ICUs), for example, 392 DDD per 1,000 patient-days in Danish hospitals in 1999 (DANMAP, 2001) or in specific hospital areas such as ICUs (see above, data in WHO DDD per 1,000 patient-days) since both one inhabitant-day and one patient-day represent one person on a defined day.

3. ANTIBIOTIC RESISTANCE IN ICU

3.1. *Enterobacteriaceae*

The Gram-negative pathogens most frequently isolated from ICU infections are *Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae*, and *Pseudomonas aeruginosa*. The number of nosocomial infections caused by *Acinetobacter* spp has increased in recent years because they are intrinsically resistant to many of the commonly used antimicrobial agents. The carbapenems are more active against *E. coli* and *K. pneumoniae* than the "third-generation" cephalosporins, ceftazidime, and cefotaxime/ceftriaxone (Table 1). The prevalence of ESBL-producing strains amongst *E. coli* (0–23%) and *K. pneumoniae* (5–64%) explains the difference in activities observed between these two antimicrobial classes. ESBL production in Gram-negative bacteria may confer resistance to virtually all commonly prescribed β-lactam antimicrobials, with the exception of the carbapenems (Table 1).

A substantial increase in the levels of ciprofloxacin resistance in *E. coli* and *K. pneumoniae* can be seen (Table 1). This is a cause for concern, especially as these species are the most frequently isolated *Enterobacteriaceae* in the ICU and can harbour ESBLs.

The resistance of *E. cloacae* to ceftazidime (19–68%—Table 1) is probably due to either the selection of Enterobacter strains producing stable derepressed constitutive chromosomal class I lactamases which hydrolyse most β-lactam antibiotics (except carbapenems which show 0–6% resistance), or the spread of Enterobacter strains, producing ESBL. The high level of use of β-lactam antibiotics such as amoxicillin, and second- and third-generation cephalosporins probably explains the increased endemic prevalence of Enterobacter producing class I β-lactamases. This endemic situation is also seen in Northern Europe (Table 1).

An alarmingly high resistance to ciprofloxacin (31%) in *Enterobacter* spp was seen in ICUs in Belgium in 1994–5 and in a European study in 1999 (20%)

(Table 1). Quinolone resistance was markedly lower in a European study in 2001 (9%) and in Belgium in 2002 (9%) (Table 1). Ciprofloxacin resistance was lower (0–9%) in Germany, Spain, Sweden, and Turkey (Table 1).

The explanation for this may differ between these countries and may depend on low total quinolone consumption, more appropriate quinolone use, the regional emergence and spread of epidemic multiresistant strains of *Enterobacter aerogenes*, or better hygiene routines in hospitals, thereby preventing outbreaks of quinolone-resistant *Enterobacter* spp. Carbapenems are the most active agents against *Enterobacter* spp (Table 1).

3.2. Non-fermentative Gram-negative bacilli

The non-fermentative Gram-negative bacilli, *Acinetobacter* spp and *P. aeruginosa*, generally show lower levels of susceptibility than the *Enterobacteriaceae* to all antimicrobials. Imipenem and meropenem have a markedly wider spectrum than other antibiotics when tested against *Acinetobacter* spp. Against *P. aeruginosa*, imipenem and meropenem also exhibit relatively high activity, with meropenem having higher activity than imipenem (Table 1). Piperacillin/tazobactam and ceftazidime were also active against many *P. aeruginosa* (Table 1). An increase in quinolone and carbapenem resistance among *P. aeruginosa* was seen in some studies (Table 1).

3.3. Coagulase-negative staphylococci (CoNS)

CoNS are low virulence pathogens. However, over the past two decades, CoNS have been increasingly recognised as a prevalent cause of nosocomial infection. For example, the NNIS and SCOPE studies rank CoNS as the most common cause of nosocomial bloodstream infection in US ICUs (Edmond *et al*., 1999; Fridkin *et al*., 1999) and the EPIC study found CoNS to be the fourth most common cause of nosocomial infection when all sites of infection were considered (Vincent *et al*., 1995). Unfortunately, antimicrobial treatment of CoNS is complicated by very high rates of oxacillin resistance worldwide. The EPIC study, carried out in 1992 in 17 Western European countries, demonstrated a 70% rate of oxacillin resistance in CoNS (Vincent *et al*., 1995). More recent data from a European study revealed higher rates of oxacillin resistance in CoNS from ICUs (88%) than non-ICUs (74%) (Rodriguez-Villabos *et al*., 2000). North American data from 2001 revealed 84% of CoNS to be oxacillin resistant (Stephen *et al*., 2002). In a study performed in 1999–2000 at 16 Nordic centres, 68% of CoNS from ICU patients were oxacillin resistant, but that was the case for only 33% of CoNS collected from patients at primary care centres (Hanberger and Nilsson, 2000). Most oxacillin-resistant CoNS are

Table 1. Surveillance of antibiotic resistance in European ICUs

Escherichia coli						
Reference	Hanberger *et al*. (1999a)	MYSTIC (2003)	Ruckdeschel *et al*. (1998)	MYSTIC (2003)	Hanberger *et al*. (1999a)	MYSTIC (2003)
Country	Belgium	Belgium	Germany	Germany	Spain	Spain
Year	1994–5	1997–2002	1996–7	1997–2002	1994–5	1997–2002
NCCLS breakpoints	I + R	I + R	R	I + R	I + R	I + R
Ceftazidime	4	6*	0	8*	1	5*
Ceftriaxone/ Cefotaxime	2	5*	0	2*	2	2*
Ciprofloxacin	6	10	6	15	14	20
Gentamicin	4	5	4	7	7	4
Imipenem	1	0	0	0	0	0
Meropenem	—	0	—	0	—	0
Piperacillin–tazobactam	15	2	3	3	4	2
***Enterobacter* spp**						
Species	*Enterobacter* spp	*E. cloacae*	*E. cloacae*	*E. cloacae*	*Enterobacter* spp	*E. cloacae*
Year	1994–5	1997–2002	1996–7	1997–2002	1994–5	1997–2002
Ceftazidime	43	20	27	26	31	19
Ceftriaxone/Cefotaxime	37	20	—	26	30	24
Ciprofloxacin	31	3	0	3	4	1
Gentamicin	3	4	—	3	4	0
Imipenem	3	0	—	0	2	0
Meropenem	—	0	—	1	—	0
Piperacillin–tazobactam	51	13	—	14	23	16
***Klebsiella* spp**						
Species	*K. pneumoniae*	*K. pneumoniae*	*Klebsiella* spp	*K. pneumoniae*	*K. pneumoniae*	*K. pneumoniae*
Year	1994–5	1997–2002	1996–7	1997–2002	1994–5	1997–2002
Ceftazidime	3	17*	1	19*	4	6*
Ceftriaxone/Cefotaxime	6	15*	1	9*	4	10*
Ciprofloxacin	1	3	4	14	2	3
Gentamicin	2	9	2	10	5	7
Imipenem	0	0	0	0	0	0
Meropenem	—	0	—	0	—	0
Piperacillin–tazobactam	14	7	10	13	3	1
Pseudomonas aeruginosa						
Year	1994–5	1997–2002	1996–1997	1997–2002	1994–1995	1997–2002
Ceftazidime	11	14	2	5	16	9
Ciprofloxacin	16	59	13	16	14	10
Gentamicin	23	12	—	23	18	11
Imipenem	16	17	7	5	22	20
Meropenem	—	10	—	3	—	3
Piperacillin–tazobactam	13	14	4	4	8	10
***Acinetobacter* spp**						
Species	*Acinetobacter* spp	*A. baumannii*	*A. baumannii*	*A. baumannii*	*Acinetobacter* spp	*A. baumannii*
Year	1994–5	1997–2002	1996–1997	1997–2002	1994–5	1997–2002
Ceftazidime	18	14	3	3	76	80
Ciprofloxacin	18	19	15	5	81	90
Gentamicin	18	14	—	4	81	86
Meropenem	—	2	—	0	—	11
Imipenem	12	2	—	0	16	18
Piperacillin–tazobactam	36	12	0	2	58	79

*ESBL phenotype by NCCLS criteria.

Hanberger *et al*. (1999a) Sweden	MYSTIC (2003) Sweden	Aksaray *et al*. (2000) Turkey	MYSTIC (2003) Turkey	Mathai *et al*. (2000) Europe	Garcia-Rodriguez and Jones (2002) Europe	Mathai *et al*. (2000) USA	Stephen *et al*. (2002) USA
1997	1997–2002	1997	1997–2002	1999	2000	1997–9	2001
I + R	I + R	I + R	I + R	I + R	I + R	R	I + R
1	2*	26	23*	9	13	3*	8*
1	0*	25	27*	4	—	2*	4*
2	5	19	38	11	16	3	13
0	4	22	23	6	8	3	8
0	0	1	1	0	<1	0	0
—	0	—	2	—	<1	—	0
4	4	35	31	11	15	5	5
Enterobacter spp	*E. cloacae*	*Enterobacter* spp	*E. cloacae*	*Enterobacter* spp	*E. cloacae*	*Enterobacter* spp	*Enterobacter* spp
1997	1997–2002	1997	1997–2002	1999	2000	1997–9	2001
19	22	68	42	40	53	33	28
30	—	70	39	37	—	30	23
3	1	8	9	20	9	6	11
0	0	44	—	9	14	9	4
0	0	4	0	6	1	< 1	2
—	0	—	0	—	1	—	2
17	18	72	35	37	49	27	26
Klebsiella spp	*K. pneumoniae*	*Klebsiella* spp	*K. pneumoniae*	*Klebsiella* spp	*K. pneumoniae*	*Klebsiella* spp	*Klebsiella* spp
1997	1997–2002	1997	1997–2002	1999	2000	1997–9	2001
1	5*	73	64*	39*	41	10*	16*
1	—	69	57*	37*	—	10*	15*
4	4	30	34	24	22	7	15
2	1	66	55	36	27	6	10
0	0	3	<1	0	1	0	0
—	0	—	4	—	1	—	0
10	3	76	50	32	32	9	10
1997	1997–2002	1997	1997–2002	1999	2000	1997–9	2001
2	11	57	56	29	29	24	23
8	26	56	61	40	45	20	30
14	6	70	81	44	46	15	19
16	18	52	57	38	36	15	22
—	11	—	50	34	31	—	20
0	10	53	44	36	19	12	13
Acinetobacter spp	*A. baumannii*	*Acinetobacter* spp	*A. baumannii*	*Acinetobacter* spp	*A. baumannii*	*Acinetobacter*	*Acin baumannii*
1994–5	1997–2002	1997	1997–2002	1999	1997–2000	spp 1997–9	2001
0	5	88	80	79	65	43	43
19	10	67	78	78	66	41	47
0	5	83	94	81	65	41	47
—	0		42	—	20	—	21
19	5	44	47	58	18	7	19
56	29	89	85	78	72	36	41

resistant to many other antimicrobial classes (Diekema *et al*., 2001), which no doubt has contributed to the widespread use of glycopeptides in the hospital setting. Glycopeptide resistance has been well described in CoNS (Schwalbe *et al*., 1987), but appears to be relatively uncommon in contemporary surveillance studies. Of over 6,000 strains of CoNS collected between 1997 and 1999 from centres worldwide, none were resistant to vancomycin, 1.9% had a vancomycin MIC of 4 μg/ml, and 1.9% were resistant to teicoplanin (MIC 16 μg/ml) (Diekema *et al*., 2001). Of the isolates collected from European centres, only 9 of 2,068 CoNS strains (0.4%) were resistant to teicoplanin and none were resistant to vancomycin (Diekema *et al*., 2001). As rates of glycopeptide resistance rise, the use of newer agents for treatment of resistant Gram-positive pathogens will increase. Three years of SENTRY surveillance (1997–9) revealed 99.9% of CoNS to be inhibited by 4 μg/ml of linezolid, while 99% were inhibited by 1 μg/ml of quinupristin/dalfopristin (Diekema *et al*., 2001).

3.4. *Staphylococcus aureus*

S. aureus is one of the most virulent of human bacterial pathogens. Since the emergence of the first oxacillin-resistant *S. aureus* (ORSA) strains in the early 1960s, the spread of ORSA has been reported in Europe and throughout the world. In the EPIC study, 60% of *S. aureus* isolates causing ICU infections were oxacillin resistant (Vincent *et al*., 1995). However, the prevalence of ORSA varied widely from country to country, with national oxacillin resistance rates of approximately 80% in Italy and France, 77% in Greece, 67% in Portugal and Belgium, 54% in Spain, 53% in Austria, 37% in Germany, 14% in Switzerland, 13% in Great Britain, and no oxacillin resistance detected in Norway, Holland, Sweden, or Denmark (Regnier, 1996; Vincent *et al*., 1995). Voss *et al*. (1994) confirmed that ORSA prevalence in many European ICUs exceeds 50% with the highest resistance rates seen in the countries of Southern Europe. In 25 European centres, mean ORSA prevalence during 1997 in all blood isolates collected from ICU patients was 39% and levels also varied widely by country (Fluit *et al*., 2001). In the 25 European centres, the mean ORSA prevalence during 1997 in all blood isolates collected from ICU patients was 39% and levels also varied widely by country. Overall, national ORSA rates ranged from $<5\%$ in Germany, Switzerland, and the Netherlands to $>50\%$ in Italy and Portugal (Fluit *et al*., 2001). These data are consistent with other data from the Netherlands and Germany that reveal low rates of oxacillin resistance in *S. aureus* (Ruckdeschel *et al*., 1998).

In other areas of Northern Europe, a recent study performed in 16 Nordic centres in 1999–2000 showed an oxacillin resistance rate in ICUs of only 3% (Hanberger and Nilsson, 2000).

In the United States, ORSA rates in *S. aureus* are high in ICUs—approximately 40% in a study performed in 1994–5 in eight geographically separate hospitals (Archibald *et al*., 1997). Data collected in 2001 reported a 51% rate of oxacillin resistance in isolates of *S. aureus* from ICU patients (Stephen *et al*., 2002). Finally, in a European study performed in 2000, Rodriguez-Villalobos *et al*. (2002) showed that 47% of *S. aureus* isolates collected from ICU patients were oxacillin resistant compared to 25% of isolates from non-ICU patients.

Most strains of ORSA are resistant to multiple drugs, but co-resistance patterns vary from region to region. Using representatives of eight different classes of antimicrobial agents (gentamicin, rifampicin, chloramphenicol, ciprofloxacin, tetracycline, clindamycin, erythromycin, and trimethoprim/sulfamethoxazole), all ORSA strains from 1997 to 1999 were examined with respect to the mean number of co-resistances by country and region (Diekema *et al*., 2001). The highest co-resistance rates were found in Latin America (mean = 4.7) and the Western Pacific (mean = 5.7). ORSA from European centres had a mean of 4.5 co-resistances: over 89% were resistant to ciprofloxacin, 83% to erythromycin, 74% to clindamycin, and 72% to gentamicin. Such high rates of co-resistance in ORSA underscore the importance of developing newer agents to treat serious infections caused by ORSA. Scattered reports of serious infections caused by ORSA with decreased susceptibility to the glycopeptides have been appearing in the literature since 1997 (CDC, 1997).

If glycopeptide resistance becomes widespread in ORSA, additional therapeutic options will be required. Fortunately, glycopeptide resistance in ORSA appears to be neither common nor widespread. Of over 15,000 clinical strains of *S. aureus* collected between 1997 and 1999 from SENTRY centres worldwide (including 3,477 strains from European centres), none were resistant to vancomycin. However, nine strains (or 0.3%) from European centres had an MIC to vancomycin of 4 μg/ml and one strain (0.03%) was resistant to teicoplanin (MIC > 16 μg/ml) (Diekema *et al*., 2001). In addition, all ORSA in this study were inhibited by 4 μg/ml of linezolid, and 98% were inhibited by 1 μg/ml of quinupristin/dalfopristin. These newer agents appear to be promising alternatives to the glycopeptides for the treatment of strains of ORSA that are resistant to multiple drugs.

The first documented case of infection caused by vancomycin-resistant *S. aureus* (VRSA) was reported in the United States in 2002 (CDC, 2002). The MIC results for vancomycin, teicoplanin, and oxacillin were >128, 32, and >16 μg/ml, respectively. The isolate contained the *vanA* vancomycin resistance gene from enterococci, which is consistent with the glycopeptide MIC profiles. It also contained the oxacillin-resistance gene *mecA*. The isolate was susceptible to chloramphenicol, linezolid, minocycline, quinupristin/dalfopristin, tetracycline, and trimethoprim/sulfamethoxazole.

3.5. Enterococci

The incidence of resistance among *Enterococcus faecium* was 10% for vancomycin, 7% for teicoplanin, 53% for ampicillin, and 30% for aminoglycoside (high-level resistance) according to a study performed in 1997–8 in 25 European hospitals (Fluit *et al*., 2001). No glycopeptide resistance, less than 1% ampicillin resistance and 32% high-level aminoglycoside resistance was seen among *Enterococcus faecalis*, which were isolated five times more frequently than *E. faecium* (Fluit *et al*., 2001). No vancomycin-resistant enterococci (VRE) were seen in *Enterococcus* spp collected in a European study in 1999 (Mathai *et al*., 2000). Similarly, a study performed in ICUs in 16 Nordic centres in 1999–2000 showed a VRE prevalence below 1% (Hanberger and Nilsson, 2000). Data collected in 2001 from European ICUs showed a 3% rate of VRE in isolates of *E. faecalis* from ICU patients compared to 1% VRE in non-ICUs (Rodriguez-Villabos *et al*., 2002).

The VRE problem is more widespread in North American ICUs according to the study carried out by Fridkin *et al*. (1999) in 1996–7, showing an overall VRE prevalence in ICUs in the United States of 13% which is higher than that reported in the study carried out in 1994–5 by Archibald *et al*. (1997). In a more recent study performed during 2001 in North American ICUs, Stephen *et al*. (2002) found 28% VRE among *Enterococcus* spp.

4. IMPROVING ANTIBIOTIC PRESCRIBING

4.1. The impact of antibiotic policies and antibiotic consumption on antibiotic resistance

Controlling antibiotic resistance requires not only improved antibiotic usage but also better compliance with infection control practices—in particular, hand disinfection. Emergence of antibiotic resistance in the ICU setting may be due to the development of resistance during therapy, or to the selection and overgrowth of preexisting resistant flora. These processes can be prevented by reducing the use of antibiotics, selecting narrow-spectrum drugs with low ecological impact, or by using bactericidal drugs that discourage mutations. However, the spread of resistant clones of, for example, MRSA, ESBL, or VRE from patients already colonised or infected with these resistant bacteria on admission or acquired within the ICU (Bonten and Mascini, 2003) has to be controlled by hygiene measures such as isolation and improved hand hygiene. Various strategies have been tried to limit antibiotic resistance (Diaz and Rello, 2002). However, some basic requirements must first be met and

these are: reducing unnecessary use of antibiotics, selecting the proper dose, frequency, route of administration and duration of treatment, and monitoring drug levels, when appropriate.

Adverse outcomes resulting from inadequate antimicrobial treatment of infections caused by antibiotic-resistant bacteria have been shown in studies by Kollef *et al*. (1998, 1999) and Zaidi *et al*. (2002). As resistance patterns change, physicians need to re-evaluate standard therapies to ensure appropriate antibiotic coverage. However, it is important to have quality control of anti-biotic therapy and all ICUs need locally adapted guidelines for the prudent use of antibiotics, including restricted use of prophylactic and therapeutic antibiotics which affect local resistance patterns (Albrich *et al*., 1999). The use of SDD has been associated with the emergence of antibiotic-resistant bacterial strains, limiting its usefulness. The routine use of SDD has not been advocated because individual trials have failed to demonstrate any reduction in mortality (Bonten *et al*., 2003; Kollef, 2003). However, a recent Dutch study has shown improved patient survival and lower prevalence of antibiotic resistance in ICU-patients receiving SDD (de Jonge *et al*., 2002), but the findings are under debate and need to be confirmed. Moreover, as the prevalence of antibiotic resistance is very low in the Netherlands compared to Southern Europe and the Americas, the extrapolation of the resistance findings to ICUs in other countries may not be valid (Bonten *et al*., 2003).

Several studies have shown that antimicrobial control has a beneficial effect on resistance patterns. Indeed, a recent study has reported the results of a new programme of antibiotic strategy control (Gruson *et al*., 2000). In that study, rotation and restricted use of antibiotics in a medical ICU reduced the incidence of ventilator-associated pneumonia caused by antibiotic-resistant Gram-negative bacteria (Gruson *et al*., 2000). In addition, Burke and Pestotnik (1999) showed that a computer-assisted decision support programme for antibiotic prescribing had the potential to stabilise bacterial resistance in the ICU. It is difficult to design a study that can prove that any reduction in colonisation or infections caused by antibiotic-resistant pathogens is due to a change in antibiotic policy, as it would be difficult to allow for improved compliance with hygiene instructions that could also lead to reduced cross-transmission of antibiotic resistant clones (Struelens *et al*., 1999). In a recent study, Allaouchiche *et al*. (2002) showed concomitant variations of antimicrobial use and the incidence of ICU-acquired infections due to third-generation cephalosporin-resistant Gram-negative bacilli, carbapenem-resistant Gram-negative bacilli, or MRSA over a 5-year period in a French ICU. Interestingly, the same study showed a protective effect of an increase in the use of medicated soaps plus alcoholic hand rubs on the incidence of ICU-acquired infections due to these resistant bacteria (Allaouchiche *et al*., 2002).

In the ESAP study, having a list of antibiotics subject to restricted use and reporting excellent communication between senior and junior doctors were

independent factors associated with low total antimicrobial use (Monnet *et al*., 2000). Reduction of the duration of therapy is another method of reducing antibiotic resistance (Baughman, 2002; Ibrahim *et al*., 2001; Singh *et al*., 2000).

4.2. Antibiotic cycling and their role in reducing resistance

Antibiotic cycling has been suggested as a strategy for discouraging the emergence of antimicrobial resistance. The concept is to withdraw an antibiotic or class of antibiotic from use in order to allow resistance rates to decrease or stabilise (Bonten, 2002). However, conflicting results have been reported in studies of antibiotic cycling and the results are inconclusive. In an early study of antibiotic cycling, Gerding *et al*. (1991) evaluated cycling of aminoglycosides and could demonstrate that a change to amikacin caused a 50% reduction in gentamicin resistance in Gram-negative bacteria but gentamicin resistance increased when it was reintroduced. The use of aminoglycosides also decreased during the study period. In another more recent antibiotic cycling study, Raymond *et al*. (2001) demonstrated a reduced incidence of antibiotic-resistant bacteria, but the study was not controlled for the relative contribution of decreased emergence of resistance vs control of cross transmission. Mathematical modelling may be used to design prospective cycling studies (Bonten *et al*., 2001).

4.3. IT and benchmarking to improve antibiotic prescribing

As most antibiotic use in the ICU is empirical, it is important to know the most prevalent pathogens and their local resistance patterns. These data can be easily provided via the Intranet or Internet if the clinical microbiology laboratory is computerised. Providing physicians with pathogen frequency, susceptibility data by ward level and site of infection, and patient-specific clinical information has been shown to improve antibiotic selection, control antibiotic costs, and slow the emergence of resistance (Evans *et al*., 1998; Pestotnik *et al*., 1996). The selection of antibiotics in the hospital setting is still a largely manual task and therefore fraught with potential errors (Bailey and McMullin, 2001). These include overuse of antibiotics, choice of inadequate agents, and dosage regimens. The decision process for antibiotic prescriptions in the ICU setting was investigated in a Swedish study carried out in 2000 (Hanberger *et al*., 2001b). Three of four ICU patients were treated with antibiotics (see above). Most prescriptions were strictly empirical and only 27% were based on a positive culture with or without an antibiogram, and only 8% of the

prescriptions were accompanied by a preliminary discontinuation date. In order to improve antibiotic use in the ICUs, more microbiological information as well as patient-specific clinical information must be made available to the prescriber. Improving antibiotic prescribing by using information systems is technically feasible, but commercial solutions are still suboptimal (Bailey and McMullin, 2001). Another option is to use an antibiotic stewardship team working in concert with critical care specialists in choosing optimal empirical regimens and in streamlining therapy once culture results are available (Paterson, 2003).

Interventions aimed at controlling the use of antibiotics require education and access to local data on antibiotic resistance and consumption. Therefore, a national ICU-surveillance programme, ICU-STRAMA was developed in Sweden in 1999, with the aim of aiding clinicians by providing feedback on local antibiotic consumption data and bacterial resistance patterns (ICU-STRAMA, 1999–2000). Local multidisciplinary ICU groups consisting of specialists in intensive care, infectious diseases, and infection control, as well as pharmacists, microbiologists, and others have formulated local policies using the information in the database which is easily accessible through a website. Person-to-person interactions are likely to be too time-consuming and unsustainable in the long term. By using the Internet, it will be possible to create a sustainable programme for the coordinated collection of information about antibiotic policy, antibiotic use, antibiotic resistance, infection control, and intensive care demography. The susceptibility of clinical isolates to important drugs has been high in Swedish ICUs, despite comparatively high consumption of antibiotics which may be due to the moderate ecological impact of the drugs chosen and the positive impact of hospital hygiene on the resistance rates. It is difficult to measure the effect of a bench programme such as ICU-STRAMA on antibiotic resistance in a low-level resistance ICU setting, but Fridkin *et al*. (2002) showed that monitoring antimicrobial use and resistance and promoting changes of practice in specific ICUs were associated with decreases in ICU vancomycin use and VRE prevalence.

5. INFECTION CONTROL

The effectiveness of infection control measures in the prevention and control of the spread of resistant bacteria has been convincingly demonstrated (Bergogne-Berezin, 1999; Eggimann *et al*., 2000; Lingnau and Allerberger, 1994; Souweine *et al*., 2000). Since bacteria can be transmitted on the hands of healthcare workers, the most effective way to prevent patient-to-patient spread of resistant pathogens is by maintaining good hand hygiene (Scott, 2000). Both hand washing and the use of alcohol-based hand disinfectants are effective

ways of reducing bacterial carriage on the hands of healthcare workers. However, alcohol-based hand disinfectants may provide superior efficacy and fewer barriers to healthcare worker compliance (Voss and Widmer, 1997). Pittet *et al*. (2000) recently published data suggesting a decline in nosocomial infection rates and ORSA prevalence after the introduction of these products into routine use in a large university hospital. Additional infection control measures (e.g., use of gloves and gowns) are necessary to prevent spread of pathogens like ORSA and VRE, which are known to contaminate the environment around infected or colonised patients (Boyce *et al*., 1997; Rhinehart *et al*., 1990; Srinivasan *et al*., 2002). The Center for Disease Control and Prevention publishes literature-based recommendations for the prevention and control of selected resistant bacterial pathogens (www.cdc.gov).

REFERENCES

Allaouchiche, B., Monnet, D., López-Lozano, J., Müller-Pebody, B., Ayzac, L., Tigaud, S. *et al*., 2002, Incidence of ICU-acquired infections due to antimicrobial-resistant microorganisms and relationships with antimicrobial use, infection control and workload in a French ICU. *42nd Interscience Conference on Antimicrobial Agents and Chemotherapy*. San Diego, CA, abstr. K-1346.

Aksaray, S., Dokuzoguz, Guvener, E. *et al*., 2000, Surveillance of antimicrobial resistance among Gram-negative isolates from intensive care units in eight hospitals in Turkey. *J. Antimicrob. Chemother.*, **45**, 695–699.

Albrich, W. C., Angstwurm, M., Bader, L., and Gartner, R., 1999, Drug resistance in intensive care units. *Infection*, **27**(Suppl. 2), S19–S23.

Andersen, C. T., and Meberg, A., 1999, [Drug use in a neonatal unit]. *Tidsskr Nor Lægeforen*, **119**, 197–200.

Archibald, L., Phillips, L., Monnet, D., McGowan, J. E., Tenover, F., and Gaynes, R., 1997, Antimicrobial resistance in isolates from inpatients and outpatients in the United States: Increasing importance of the intensive care unit. *Clin. Infect. Dis.*, **24**, 211–215.

Bailey, T. C. and McMullin, S. T., 2001, Using information systems technology to improve antibiotic prescribing. *Crit. Care Med.*, **29**(Suppl.), 87–91.

Baughman, R. P., 2002, Antibiotic resistance in the intensive care unit. *Curr. Opin. Crit. Care*, **8**, 430–434.

Bergmans, D. C., Bonten, M. J., Gaillard, C. A., van Tiel, F. H., van der Geest, S., de Leeuw, P. W. *et al*., 1997, Indications for antibiotic use in ICU patients: A one-year prospective surveillance. *J. Antimicrob. Chemother.*, **39**, 527–535.

Bergogne-Berezin, E., 1999, Current guidelines for the treatment and prevention of nosocomial infections. *Drugs*, **58**, 51–67.

Bonten, M. J., Austin, D. J., and Lipsitch, M., 2001, Understanding the spread of antibiotic resistant pathogens in hospitals: Mathematical models as tools for control. *Clin. Infect. Dis.*, **33**, 1739–1746.

Bonten, M. J., 2002, Infection in the intensive care unit: Prevention strategies. *Curr. Opin. Infect. Dis.*, **15**, 401–405.

Bonten, M. J., and Mascini, E. M., 2003, The hidden faces of the epidemiology of antibiotic resistance. *Intensive Care Med.*, **29**, 1–2.

Bonten, M. J., Joore, H. C., de Jongh, B. M. *et al*., 2003, Selective decontamination of the digestive tract: All questions answered? *Crit. Care*, **7**, 203–205.

Borderon, J. C., Laugier, J., Ramponi, N., Saliba, E., Gold, F., and Blond, M. H., 1992, Surveillance of antibiotic therapy in a pediatric intensive care unit. *Ann. Pediatr.* (Paris), **39**, 27–36.

Bourdain, N., Lepape, A., Galzot, F., Lamy, B., Haessler, D., Chomarat, M. *et al*., 1999, Peut-on utiliser des protocoles d'antibiothérapie probabiliste en réanimation? *Pathol. Biol.*, **47**, 584–588.

Boyce, J. M., Potter-Bynoe, G., Chenevert, C., and King, T., 1997, Environmental contamination due to methicillinresistant Staphylococcus aureus: Possible infection control implications. *Infect. Control Hosp. Epidemiol.*, **18**, 622–627.

Burke, J. P. and Pestotnik, S. L., 1999, Antibiotic use and microbial resistance in intensive care units: Impact of computer-assisted decision support. *J. Chemother.*, **11**, 530–535.

Burwen, D. R., Banerjee, S. N., Gaynes, R. P., and the National Nosocomial Infections Surveillance System, 1994, Ceftazidime resistance among selected nosocomial Gram-negative bacilli in the United States. *J. Infect. Dis.*, **170**, 1622–1625.

Capellà, D., 1993, Descriptive tools and analysis. *WHO Reg. Publ. Eur. Ser.*, **45**, 55–78.

Carmeli, Y., Eliopoulos, G., Mozaffari, E., and Samore, M., 2002, Health and economic outcomes of vancomycin-resistant enterocci. *Arch. Intern. Med.*, **162**, 2223–2228.

Cars, O., Mölstad, S., and Melander, A., 2001, Variation in antibiotic use in the European Union. *Lancet*, **357**, 1851–1853.

Centers for Disease Control and Prevention, 1997, Update: Staphylococcus aureus with reduced susceptibility to vancomycin—United States, 1997. *MMWR*, **46**, 813–815.

Centers for Disease Control and Prevention, 2002, Staphylococcus areus resistant to vancomycin—United States, 2002. *MMWR*, **51**, 565–567.

DANMAP 2000, Consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals and humans in Denmark. Danish Veterinary Laboratory. Copenhagen, Denmark. 2001. Available from http://www.dfvf.dk/Files/Filer/Zoonosecentret/Publikationer/Danmap/Danmap_2000.pdf

De Jonge, E., Schultz, M. J., Spanjaard, L. *et al*., 2002, European Society of Intensive Care Medicine, 15th Annual Congress (Barcelona): Effects of selective decontamination of the digestive tract on mortality and antibiotic resistance (abstract 30). *Intensive Care Med.*, **28**(Suppl. 1), S12.

Diaz, E. and Rello, J., 2002, Top ten list in antibiotic policy in the ICU. *Chest*, **122**, 712–714.

Diekema, D. J., Pfaller, M. A., Jones, R. N., Doern, G. V., Winokur, P. L., Gales, A. C. *et al*., and the SENTRY participants group (Americas), 1997, Survey of bloodstream infections due to gram-negative bacilli: Frequency of occurrence and antimicrobial susceptibility of isolates collected in the United States, Canada and Latin America for the Sentry antimicrobial surveillance program. *Clin. Infect. Dis.*, **29**, 595–607.

Diekema, D. J., Pfaller, M. A., Schmitz, F. J. *et al*., and the SENTRY Participants Group, 2001, Survey of infections due to Staphylococcus species: Frequency of occurrence and antimicrobial susceptibility of isolates collected in the United States, Canada, Latin America, Europe and the Western Pacific for the SENTRY Antimicrobial Surveillance Program, 1997–1999. *Clin. Infect. Dis.*, **32**(Suppl 2), S114–S132.

Eggimann, P., Harbarth, S., Constantin, M. N., Touveneau, S., Chevrolet, J. C., and Pittet, D., 2000, Impact of a prevention strategy targeted at vascular-access care on incidence of infections acquired in intensive care. *Lancet*, **355**, 1864–1868.

Edmond, M. B., Wallace, S. E., McClish, D. K., Pfaller, M. A., Jones, R. N., and Wenzel, R. P., 1999, Nosocomial bloodstream infections in United States hospitals: A three-year analysis. *Clin. Infect. Dis.*, **29**, 239–244.

Erlandsson, C.-M., Hanberger, H., Eliasson, I., Hoffmann, M., Isaksson, B., Lindgren, S. *et al*., 1999, Surveillance of antibiotic resistance in ICUs in south-eastern Sweden. *Acta Anaesthesiol. Scand.*, **43**, 815–820.

Evans, R. S., Pestotnik, S. L., Classen, D. C., *et al*., 1998, A computer-assisted management program for antibiotics and other anti-infective agents. *N. Engl. J. Med.* **338**, 232–238.

Fischer, J. E., Ramser, M., and Fanconi, S., 2000, Use of antibiotics in pediatric intensive care and potential savings. *Intensive Care Med.*, **26**, 959–966.

Fonseca, S. N., Ehrenkranz, R. A., and Baltimore, R. S., 1994, Epidemiology of antibiotic use in a neonatal intensive care unit. *Infect. Control Hosp. Epidemiol.*, **15**, 156–162.

Fluit, A. C., Verhoef, J., Schmitz, F. J., European SENTRY Participants, 2001, Frequency of isolation and antimicrobial resistance of gram-negative and gram-positive bacteria from patients in intensive care units of 25 European university hospitals participating in the European arm of the SENTRY antimicrobial surveillance program 1997–1998. *Eur. J. Clin. Microbiol. Infect. Dis.*, **20**, 617–625.

Fridkin, S. K., Steward, C. D., Edwards, J. R., Pryor, E. R., McGowan, J. E., Jr., Archibald, L. K. *et al*., 1999, Surveillance of antimicrobial use and antimicrobial resistance in United States hospitals: Project ICARE phase 2. *Clin. Infect. Dis.*, **29**, 245–252.

Fridkin, S. K., Lawton, R., Edwards, J. R., Tenover, F. C., McGowan, J. E., Gaynes, R. P., the Intensive Care Antimicrobial Resistance Epidemiology (ICARE) Project, and the National Nosocomial Infections Surveillance (NNIS) system hospitals, 2002, Monitoring antimicrobial use and resistance: Comparison with a national benchmark on reducing vancomycin use and vancomycin-resistant enterococci. *Emerg. Infect. Dis.*, **8**, 702–707.

Garcia-Rodriguez, J. A. and Jones, R. N., 2002, Antimicrobial resistance in gram-negative isolates from European intensive care units: Data from the Meropenem Yearly Susceptibility Test Information Collection (MYSTIC) programme. *J. Chemother.*, **14**, 25–32.

Gastmeier, P., Sohr, D., Forster, D., Schulgen, G., Schumacher, M., Daschner, F. *et al*., 2000, Identifying outliers of antibiotic usage in prevalence studies on nosocomial infections. *Infect. Control Hosp. Epidemiol.*, **21**, 324–328.

Gerding, D. N., Larson, T. A., Hughes, R. A. *et al*., 1991, Aminoglycoside resistance and aminoglycoside usage: Ten years of experience in one hospital. *Antimicrob. Agents. Chemother.*, **35**, 1284–1290.

Gortner, L., 1993, Drug utilisation in preterm and term neonates. *Pharmacoeconomics*, **4**, 437–445.

Grupo de Trabajo de Enfermedades Infecciosas de la Sociedad Española de Medicina Intensiva y Unidades Coronarias (GTEI-SEMIUC). ENVIN-UCI, Estudio Nacional de Vigilancia de Infeccion Nosocomial en Servicios de Medicina Intensiva. Informe 1996.

Gruson, D., Hilbert, G., Vargas, F., Valentino, R., Bebear, C., Allery, A. *et al*., 2000, Rotation and restricted use of antibiotics in a medical intensive care unit. Impact on the incidence of ventilator-associated pneumonia caused by antibiotic-resistant gram-negative bacteria. *Am. J. Respir. Crit. Care Med.*, **162**, 837–843.

Hanberger, H., Garcia-Rodriguez, J. A., Gobernado, M., Goossens, H., Nilsson, L. E., and Struelens, M. J., 1999a, Antibiotic susceptibility among aerobic Gram-negative bacilli in intensive care units. *JAMA*, **281**, 67–71.

Hanberger, H., Nilsson, L. E., Claesson, B. *et al*., 1999b, New species-related MIC breakpoints for early detection of development of resistance among Gram-negative bacteria in Swedish intensive care units. *J. Antimicrob. Chemother.*, **44**, 611–619; **35**, 152–160.

Hanberger, H., Nilsson, L. E., and the SCOPE study Group, 2000, May, Higher incidence of antibiotic resistance among nosocomial bacteria in Nordic intensive care units (ICUs) compared to primary care centres. Abstracts of the 3rd European Congress of Chemotherapy, Madrid, Abstr. T 136.

Hanberger, H., Diekema, D., Fluit, A., Jones, R., Struelens, M., Spencer, R. *et al*., 2001a, Surveillance of antibiotic resistance in European ICUs 2001a, *J. Hosp. Infect.*, **48**, 161–176.

Hanberger, H., Erlandsson, M., Burman, L. G., Cars, O., Gill, H., Lindgren, S., Nilsson, L. E., Olsson-Liljequist, B., Walther, S., and ICU-Strama Study Group, 2004, High Antibiotic Susceptibility among Bacterial Athogens in Swedish ICUs, *Scand. J. Infect. Dis*., **36**, 24–30.

Ibrahim, E. H., Ward, S., Sherman, G. *et al*., 2001, Experience with a clinical guideline for the treatment of ventilator-associated pneumonia. *Crit. Care Med.*, **29**, 1109–1115.

ICU-STRAMA 1999–2000, Surveillance of antibiotic consumption and antibiotic resistance and its relationship to severity of illness and infection control in Swedish intensive care units. Available from http://dior.imt.liu.se/icustrama/

Intensive Care Antimicrobial Resistance Epidemiology (ICARE) Surveillance Report, 1999, June, Data Summary from January 1996 through December 1997, A report from the National Nosocomial Infections Surveillance (NNIS) System. *Am. J. Infect. Control*, **27**, 279–284.

Kiivet, R. A., Dahl, M. L., Llerena, A., Maimets, M., Wettermark, B., and Berecz, R., 1998, Antibiotic use in 3 European university hospitals. *Scand. J. Infect. Dis.*, **30**, 277–280.

Kollef, M. H., and Ward, S., 1998, The influences of mini-BAL cultures on patient outcomes: Implications for antibiotic management of ventilator-associated pneumonia. *Chest*, **113**, 412–420.

Kollef, M. H., Sherman, G., Ward, S., and Fraser, V. J., 1999, Inadequate antimicrobial treatment of infections: A risk factor for hospital mortality among critically ill patients. *Chest*, **115**, 462–474.

Kollef, M. H., Ward, S., Sherman, G., Prentice, D., Schaiff, R., Huey, W. *et al*., 2000, Inadequate treatment of nosocomial infections is associated with certain empiric antibiotic choices. *Crit. Care Med.*, **28**, 3456–3464.

Kollef, M. H., 2003, Selective digestive decontamination should not be routinely employed. *Chest*, **123**(Suppl.), 464S–468S.

Lemmen, S. W., Häfner, H., Kotterik, S., Lütticken, R., and Töpper, R., 2000, Influence of an infectious disease service on antibiotic prescription behavior and selection of multiresistant pathogens. *Infection*, **28**, 384–387.

Lingnau, W. and Allerberger, F., 1994, Control of an outbreak of methicillin-resistant Staphylococcus aureus (MRSA) by hygienic measure in a general intensive care unit. *Infection*, **22**(Suppl. 2), S135–S139.

Mathai, D., Jones, J. N., Stilwell, M., and Pfaller, M. A., 2000, Three year analysis of pathogen occurrence and antimicrobial resistance in 315 intensive care units within 71 participating medical centres (32 nations). Report from the SENTRY antimicrobial surveillance program (1997–99). Presented in part at the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy, Toronto, Session 108, Poster 1027.

Monnet, D. L., Suetens, C., Jepsen, O. B., Burman, L. G., Carsauw, H., Gastmeier, P. *et al*., and the European Strategy for Antibiotic Prophylaxis (ESAP) Project Team, 2000, Overall antimicrobial use and control strategies in intensive care units from 6 European countries. 4th Decennial International Conference on Nosocomial and Healthcare-Associated Infections, Atlanta, GA, 2000, abstr. P-S2-03. *Infect. Control Hosp. Epidemiol.*, **21**, 88.

MYSTIC (AstraZeneca, data on file), 2003.

Naaber, P., Kõljalg, S., and Maimets, M., 2000, Antibiotic usage and resistance—trends in Estonian University Hospitals. *Int. J. Antimicrob. Agents*, **16**, 309–315.

Paterson, D. L., 2003, Restrictive antibiotic policies are appropriate in intensive care units. *Crit. Care Med.*, **31**(Suppl.), S25–S28.

Pestotnik, S. L., Classen, D. C., Evans, R. S. *et al*., 1996, Implementing antibiotic practice guidelines through computer-assisted decision support: Clinical and financial outcomes. *Ann. Intern. Med.*, **124**, 884–890.

Petersen, I. S., Hesselbjerg, L., Jørgensen, L., Renstrup, J., Barnung, S., Schierbeck, J. *et al*., 1999, High antibiotic consumption in Danish intensive care units? *APMIS*, **107**, 989–996.

Pittet, D., Hugonnet, S., Harbarth, S. *et al*., 2000, Effectiveness of a hospital-wide programme to improve compliance with hand hygiene. *Lancet*, **356**, 1307–1312.

Raymond, D. P., Pelletier, S. J., Crabtree, T. D. *et al*., 2001, Impact of rotating empiric antibiotic schedule on infectious mortality in an intensive care unit. *Crit. Care Med.*, **29**, 1101–1108.

Regnier, B., 1996, Epidemiology on control of antibiotic multiresistant bacteria in hospitals (in French). *Path. Biol.*, **44**, 113–123.

Rhinehart, E., Smith, N. E., Wennersten, C. *et al*., 1990, Rapid dissemination of beta-lactamase producing aminoglycoside resistant Enterococcus faecalis among patients and staff on an infant-toddler surgical ward. *N. Engl. J. Med.*, **323**, 1814–1818.

Røder, B. L., Nielsen, S. L., Magnussen, P., Engquist, A., and Frimodt-Møller, N., 1993, Antibiotic usage in an intensive care unit in a Danish university hospital. *J. Antimicrob. Chemother.*, **32**, 633–642.

Rodriguez-Villalobos, H., Jones, R., and Struelens, M. J., 2002, Epidemiology of antibiotic resistance of bacterial pathogens from intensive care units: The SENTRY surveillance program in Europe 2000. *Clin. Microbiol. Infect.*, **8**(Suppl. 1), Abstract: P908.

Ruckdeschel, G., Grimm, H., Machka, K., and Wiedemann, B., 1998, Comparison of antibiotic resistance in clinical bacterial strains from general wards vs. intensive care unit patients. In *Abstracts of the 2nd European Congress of Chemotherapy*. Hamburg, Abstract T253.

Scott, G., 2000, Prevention and control of infections in intensive care. *Intensive Care Med.*, **26**(Suppl. 1), S22–S25.

Schwalbe, R. S., Stapleton, J. T., and Gilligan, P. H., 1987, Emergence of vancomycin resistance in coagulase-negative staphylococci. *N. Engl. J. Med.*, **316**, 927–931.

Singh, N., Rogers, P., Atwood, C. W. *et al*., 2000, Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit. A proposed solution for indiscriminate antibiotic prescription. *Am. J. Respir. Crit. Care Med.*, **162**, 505–511.

Souweine, B., Traore, O., Aublet-Cuvelier, B. *et al*., 2000, Role of infection control measures in limiting morbidity associated with multi-resistant organisms in critically ill patients. *J. Hosp. Infect.*, **45**, 107–116.

Srinivasan, A., Song, X., Ross, T., Merz, W., Brower, R., and Perl, T. M., 2002, A prospective study to determine whether cover gowns in addition to gloves decrease nosocomial transmission of vancomycin-resistant enterococci in an intensive care unit. *Infect. Control Hosp. Epidemiol.*, **23**, 424–428.

Stephen, J., Mutnick, A., and Jones, R. N., 2002, Assessment of pathogens and resistance (R) patterns among intensive care unit (ICU) patients in North America (NA): Initial Report from the SENTRY Antimicrobial Surveillance Program (2001). *42nd Interscience Conference on Antimicrobial Agents and Chemotherapy*. San Diego, Abstract: C2-297.

Struelens, M. J., Byl, B., and Vincent, J. L., 1999, Antibiotic policy: A tool for controlling resistance of hospital pathogens. *Clin. Microbiol. Infect.*, **5**, S19–S24.

Tarp, B. D., and Møller, J. K., 1997 [Utilization of antibiotics at the Arhus Municipal Hospital. A prevalence study]. *Ugeskr Laeger*, **159**, 936–939.

Tullus, K., Berglund, B., Fryklund, B., Kühn, I., and Burman, L. G., 1988, Epidemiology of fecal strains of the family Enterobacteriaceae in 22 neonatal wards and influence of antibiotic policy. *J. Clin. Microbiol.*, **26**, 1166–1170.

Vlahovic-Palcevski, V., Morovic, M., and Palcevski, G., 2000, Antibiotic utilization at the university hospital after introducing an antibiotic policy. *Eur. J. Clin. Pharmacol.*, **56**, 97–101.

Vincent, J. L., Bihari, D. J., Suter, P. M., Bruining, H. A., White, J., Nicolas-Chanoin, M.-H. *et al*., 1995, The prevalence of nosocomial infection in intensive care units in Europe. *JAMA*, **274**, 639–644.

Voss, A., Milatovic, D., Wallrauch-Schwarz, C. *et al*., 1994, Methicillin-resistant Staphylococcus aureus in Europe. *Eur. J. Clin. Microbiol. Infect. Dis.*, **13**, 50–55.

Voss, A. and Widmer, A. F., 1997, No time for handwashing!? Handwashing versus alcoholic rub: Can we afford 100% compliance? *Infect. Control Hosp. Epidemiol.*, **18**, 205–208.

Walther, S. M., Erlandsson, M., Burman, L. G., Cars, O., Gill, H., Hoffman, M. *et al*., and the Icustrama Study Group, 2002, Antibiotic prescription practices, consumption and bacterial resistance in a cross section of Swedish intensive care units. *Acta Anaesthesiol. Scand.*, **46**, 1075–1081.

White, R. L., Friedrich, L. V., Mihm, L. B., and Bosso, J. A., 2000, Assessment of the relationship between antimicrobial usage and susceptibility: Differences between the hospital and specific patient-care areas. *Clin. Infect. Dis.*, **31**, 16–23.

Zaidi, M., Sifuentes-Osornio, J., Rolon, A. L. *et al*., 2002, Inadequate therapy and antibiotic resistance. Risk factors for mortality in the intensive care unit. *Arch. Med. Res.*, **33**, 290–294.