International Journal of Infection Control
ISSN 1816-6296 Vol. 3 Issue 1

Original article

Surveillance of Antimicrobial Resistance in Intensive Care Setting at St Luke's Hospital, Malta

Elizabeth Anne Scicluna[1*], Hakan Hanberger[2]

[1] Infection Control Unit, St. Luke's Hospital, G'Mangia MSD08, Malta
[2] Swedish Institute of Infectious Disease Control, Solna and Faculty of Health Sciences, Linköping, Sweden

Int J Infect Contr 2007, **3**:1 doi:10.3396/03-01-14-07 Available from: http://www.ijic.info

Abstract

Knowing the resistance profile for the most common organisms that cause infections in a specific intensive care setting can help in guiding the intensivists when giving empiric antibiotic treatment, since adequate and timely treatment is of utmost importance to save lives. The main Intensive Care Unit (ICU) in St Luke's Hospital is a 13-bed case-mixed ward, with 97% annual occupancy rate. To improve surveillance and control antibiotic resistance, we participated in Care-ICU (Controlling Antibiotic REsistance in ICU), a program for infection control surveillance part of the IPSE (Improving Patient Safety in Europe) project. The most common organisms isolated were *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Staphylococcus aureus*. However, in blood cultures *Enterococcus faecalis* was third in 2005 and second in 2006, preceded only by *P. aeruginosa*. In respiratory specimen there was a shift from *P. aeruginosa*, with 33% of isolates in 2005 and 24% in 2006, to *A. baumannii* from 22% to 34%.

Frequency of antibiotic resistance varies between species and sources. In blood, oxacillin resistance in *S. aureus* reached 86%. In *P. aeruginosa* and *A. baumannii* resistance to carbapenem was 19% and 86% and for 3rd generation cephalosporins was 44% and 85% respectively. Meropenem is the most common antibiotic used in this ICU with 1997.5 defined daily doses (DDD) in 2006. Several 3 rd generation cephalosporins are used including ceftriaxone (629 DDD), ceftazidime (139.8 DDD) and cefotaxime (49.5 DDD). Resistance rates in our ICU are very high when compared to other centres participating in CARE-ICU, for example the median resistance rate for carbapenem in *A. baumannii* is 12%. Feedback on antimicrobial resistance may be a useful tool to tackle misuse of antibiotics and emergence of antibiotic resistance. There is an urgent need for increased compliance to hygiene rules and improved infection control and the most efficient infection control interventions have to be defined.

Introduction

Nosocomial infections, especially with antimicrobial-resistant organisms, are a major problem in intensive care units (ICU)[1] and the increasing prevalence of these antibiotic-resistant strains is of concern, with more than 60% of *Staphylococcus aureus* isolates recovered from the ICU being resistant to methicillin (methicillin-resistant *Staphylococcus aureus* [MRSA])[2]. Routine surveillance for MRSA in ICUs allows for earlier initiation of contact isolation precautions and is associated with large and statistically significant reductions in the incidence of MRSA bacteraemia in the ICUs and hospital wide[3]. MRSA appears to be associated with worse outcomes than methicillin-sensitive *S. aureus* (MSSA) infection. It was reported that MRSA bacteraemia increase significantly the risk for death compared with MSSA bacteraemia[4].

Corresponding author:
Elizabeth Anne Scicluna, Infection Control Unit, St. Luke's Hospital, G'Mangia MSD08, Malta
Email: elizabeth.a.scicluna@gov.mt

Among critically ill patients in the ICU, *Acinetobacter spp*. cause serious infections, the management of which is complicated by antimicrobial resistance, including carbapenem resistance. Multidrug-resistant *Acinetobacter baumannii* (MDR-Ab) has emerged as an increasingly problematic cause of hospital-acquired infections in the ICU. MDR-Ab is resistant to most standard antimicrobials but often retains susceptibility to polymyxin B and doxycycline[5]. Therapy cycling between various classes of empiric antibiotics in intensive care environments may influence bacterial resistance patterns. Understanding the impact of cycling on the appropriate treatment of suspected Gram-negative infections is important. Antimicrobial resistance occurred in almost 30% of ICU infections involving Gram-negative bacteria[1].

Early broad-spectrum antibiotic administration decreases morbidity and mortality and should be based on knowledge of the sensitivities of common infecting organisms in the ICU[6]. De-escalation of therapy, once final culture results are available, is necessary to minimize development of resistant pathogens. Duration of therapy should be based on the patient's clinical response, and every effort should be made to minimize duration of therapy, thus further minimizing the risk of resistance. The intensivist treating the patient will need to have a clear knowledge of the ambient microbiologic flora in their ICU. Patients receiving inappropriate empiric therapy, because the bacterial isolate is resistant to the drug used, are more likely to die[1]. Therapy cycling empiric antibiotics between various classes may influence bacterial resistance patterns.

In this study, the most frequent organism causing bacterial infections and their resistance profiles were determined for patients admitted to the ICU over the years 2005-2006.

Methods

The main ICU in St Luke's Hospital, Malta, is a 13-bed case-mixed ward, with 97% occupancy rate. Surveillance data was collected according to the Care-ICU (Controlling Antibiotic REsistance in ICU) protocol (http://www4.smittskyddsinstitutet.se/careicu). CARE-ICU is a program for infection control surveillance, which is part of the IPSE (Improving Patient Safety in Europe) project (http://helics.univ-lyon1.fr/). CARE-ICU is a web-based programme aiming to improve surveillance and control of antibiotic resistance, the use of antibiotic and hygienic precautions in the ICU setting of EU Member States. It was developed for use in Swedish ICUs and than revised and approved to ensure fitness for implementation in EU ICUs. A unique user name and password were given by the project co-ordinators to one national administrator, who in turn gave access to various assistants. The national administrator has the possibility to give different access rights to each assistant involved in the project depending on their use of the database.

Part of this surveillance included the species distribution in all specimens and also for blood, urine and respiratory tract specimen to see which are the most prevalent organisms per specimen source. The number of initial isolates per source per organism was entered into the web-based database. Another part of the surveillance was for obtaining the resistance profiles. Data entry for computing resistance profiles was done for a list of organisms. After selecting the organism, a list of antibiotics appeared, for which one needed to report the number of S (sensitive), I (intermediate) or R (resistant) for the first isolate per patient. The resistance profiles needed to be calculated for all specimens together and also for blood cultures only. From a drop down list, the guidelines used were selected. The web-based surveillance tool simplifies and secures the data registration at the ICU levels as well as at the hospital and national level. In addition, it gives the institutions faster and easier access to the results.

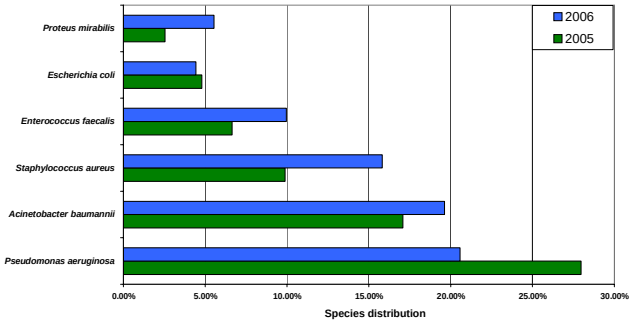

Figure 1: Species distribution for the most common organisms isolated from all specimen taken from patients in ITU for 2005 and 2006.

Results

Three bacterial species, *Pseudomonas aeruginosa, A. baumannii* and *S. aureus*, accounted for more than 55% of all ICU isolates (Figure 1). Other less prevalent bacterial isolates were *Enterococcus faecalis* and *Escherichia coli* and *Proteus mirablis*. However, in blood cultures *E. faecalis* was the third most common organism in 2005 and the second most common in 2006, preceded only by *P. aeruginosa* (Figure 2). In respiratory tract specimens

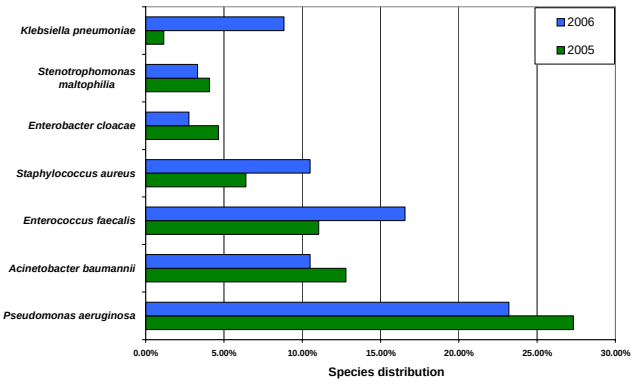

Figure 2: Species distribution for the most common organisms isolated from blood cultures taken from patients in ITU for 2005 and 2006.

there was a shift from *P. aeruginosa*, with 33% of isolates in 2005 and 24% in 2006, to *A. baumannii* from 22% to 34% (Figure 3).

Frequency of antibiotic resistance varies between species and sources and also between years (Table 1). Resistance to oxacillin in *S. aureus* is on the increase. In 2005 for all specimens from ICU 64.1% of *S. aureus* were MRSA and increased to 82% in 2006. In blood cultures, from 50% in 2005 it reached 85.7% in just one year. In *P. aeruginosa* and *A. baumannii* resistance to carbapenem was 18.5% and 85.7% and for 3rd generation cephalosporins is 44.0% and 84.6% respectively in blood for 2006, while for all specimen in the same year these were 33.3% and 93.6% resistant to carbapenem and 23.6% and 93.3% resistant to ceftazidime respectively.

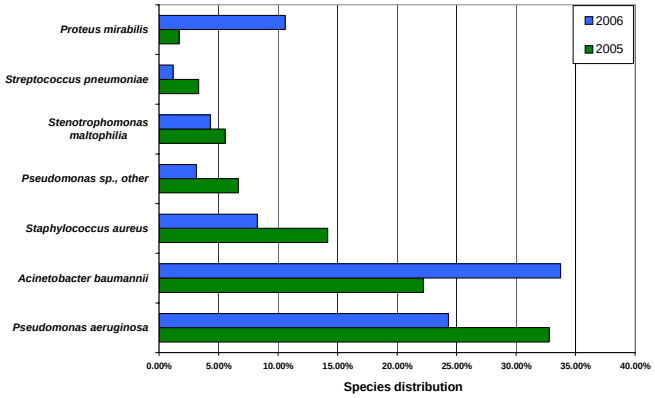

Figure 3: Species distribution for the most common organisms isolated from respiratory tract specimen taken from patients in ITU for 2005 and 2006.

Discussion:

When comparing our results with those from the CARE-ICU study[7], it is obvious that our resistance rates are much higher than most of those in the participating countries. Data from 2005 show that the median MRSA rate in the study was 22.7% and the highest rate of MRSA in CARE-ICU was reported from Turkey with 94.4% of the *S. aureus* being resistant to oxacillin. Our ICU reported 64.1% in 2005 and reached 82% in 2006. In another study carried out in Turkey, 13 ICUs participating in the National Nosocomial Infections Surveillance System (NNISS)[8], reported 89.2% of all *S. aureus* infections were caused by methicillin-resistant strains.

Infection control measures to prevent cross-transmission of methicillin-resistant *S. aureus* in intensive care units may be more effective when patients are in single rooms than when they are in bay rooms[9]. Multi-resistant bacteria are an increasing challenge for infection control in hospitals and the proportion of patients newly colonized with multi-resistant bacteria during their hospital stay can be used to assess the effectiveness of infection control measures. Mikolajczyk and colleagues, estimated that the proportion of methicillin-resistant *S. aureus* cases resulting from cross-transmission in hospital is 0.73 (95% CI: 0.56-0.90)[10].

Measures to control transmission of multiple drug resistant bacteria are complicated and costly, and their success depends on many factors[11]. Reduction in antibiotic use can reduce the emergence of resistance during antibiotic therapy but is of less importance in outbreaks of MRSA. In our ICU, meropenem is the most common antibiotic used with 1997.5 defined daily doses (DDD) in 2006, followed by clarithromycin (1068.5 DDD) and metronidazole (984.4 DDD). Several third generation cephalosporins are used, including ceftriaxone (629 DDD), ceftazidime (139.8 DDD) and cefotaxime (49.5 DDD).

Strict MRSA control measures including the “search and destroy” strategy are apparently still keeping this problem at a minimal level in ICUs in low level resistance countries, although such precautions were recently questioned by an ICU-study in the UK [12]. However, that study was criticised as isolation or cohort care on detection of MRSA was not usually performed until 3-4 days after admission. MRSA is endemic in our hospital and most especially in the ICU. Once a result of MDR organism is received the patient will be isolated in the ICU in one of 3 isolation rooms or cohorted into a 2-beded room and a decontamination process is started. For MRSA carriage decontamination is done with bactroban nasal ointment for 5 days and chlorhexidine washes for a week. When it is necessary, the antibiotic treatment is adjusted to include teicoplanin. If the patient is fit to be discharged from the ICU s/he is transferred to a cohort ward.

The experience from recent outbreaks in two large Swedish teaching hospitals showed that it is possible to eradicate an imported epidemic MRSA strain using an intensive control programme[13]. The programme, which in addition to the standard “search and destroy” policy, included increasing staff, MRSA-screening of re-admitted patients and strict adherence to cohort care of MRSA-colonised patients and closure of wards where more than one MRSA-colonised patient had been identified. Out of the three infection control nurses in our hospital, one is assigned to the ICUs. There is also an antibiotic pharmacist available to give advice on antibiotic use to those clinician that require it and most of the intensivist contact the infectious disease specialists for the proper antibiotics to administer. Patients are screened (nasal swab) for MRSA on admission to the ICU and once a week, every Monday, thereafter.

An MRSA eradication programme was also cost-effective in low-level resistance setting[13]. However, when needs exceed the available control resources, a large outbreak is always a threat and its outcome hard to predict. A recent French study reported a successful long-term programme for controlling MRSA in ICUs[14].

Table 1: Resistance profiles for *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Staphylococcus aureus* isolated from the mixed Intensive Care Unit of St Luke's Hospital in 2005 and 2006 from blood and other specimen.

Organism	Resistance profile - I + R % (95% CI)							
	2005				2006			
Antibiotic	n	Blood	n	All Specimen	n	Blood	n	All Specimen
Pseudomonas aeruginosa								
Amikacin	23	13.0 (3.4, 34.7)	53	11.3 (4.7, 23.7)	27	7.4 (1.3, 25.8)	57	7.0 (2.3, 17.8)
Ceftazidime	22	18.2 (6.0, 41.0)	52	11.5 (4.8, 24.1)	25	44.0 (25.0, 64.7)	55	23.6 (13.7, 37.3)
Ciprofloxacin	23	39.1 (20.5, 61.2)	53	24.5 (14.2, 38.6)	27	29.6 (14.5, 50.3)	57	22.8 (13.2, 36.2)
Gentamicin	23	17.4 (5.7, 39.5)	52	19.2 (10.1, 33.0)	27	7.4 (1.3, 25.8)	57	12.3 (5.5, 24.3)
Imipenem	23	34.8 (17.2, 57.2)	53	30.2 (18.7, 44.5)	27	18.5 (7.0, 38.7)	57	33.3 (21.7, 47.2)
Netilmicin	23	21.7 (8.3, 44.2)	52	23.1 (13.0, 37.2)	23	17.4 (5.7, 39.5)	50	20.0 (10.5, 34.1)
Piperacillin and enzyme inhibitor	23	30.4 (14.1, 53.0)	52	19.2 (10.1, 33.0)	23	43.5 (23.9, 65.1)	52	34.6 (22.3, 49.2)
Tobramycin	23	17.4 (5.7, 39.5)	44	11.4 (4.3, 25.4)	23	4.4 (0.2, 24.0)	51	13.7 (6.2, 26.9)
Acinetobacter baumannii								
Amikacin	16	6.3 (0.3, 32.3)	44	2.3 (0.1, 13.5)	14	7.1 (0.4, 35.8)	62	3.2 (0.6, 12.2)
Ceftazidime	16	93.8 (67.7, 99.7)	44	90.9 (77.4, 97.0)	13	84.6 (53.7, 97.3)	60	93.3 (83.0, 97.8)
Ciprofloxacin	16	93.8 (67.7, 99.7)	44	93.2 (80.3, 98.2)	14	85.7 (56.2, 97.5)	62	93.6 (83.5, 97.9)
Gentamicin	16	93.8 (67.7, 99.7)	44	93.2 (80.3, 98.2)	14	85.7 (56.2, 97.5)	62	91.9 (81.5, 97.0)
Imipenem	16	87.5 (60.4, 97.8)	44	90.9 (77.4, 97.0)	14	85.7 (56.2, 97.5)	62	93.6 (83.5, 97.9)
Netilmicin	15	60.0 (32.9, 83.5)	34	70.6 (52.3, 84.3)	4	50.0 (9.2, 90.8)	51	58.8 (44.2, 72.1)
Piperacillin and enzyme inhibitor	15	86.7 (58.4, 97.7)	39	87.2 (71.8, 95.2)	5	60.0 (17.0, 92.7)	52	90.4 (78.2, 96.4)
Tobramycin	15	86.7 (58.4, 97.7)	38	92.1 (77.5, 97.9)	6	66.7 (24.1, 94.0)	53	90.6 (78.6, 96.5)
Staphylococcus aureus								
Erythromycin	8	37.5 (10.2, 74.1)	38	50.0 (33.7, 66.3)	14	57.1 (29.6, 81.2)	33	60.6 (42.2, 76.6)
Fusidic acid	8	25.0 (4.5, 64.4)	39	41.0 (26.0, 57.8)	14	14.3 (2.5, 43.8)	32	25.0 (12.1, 43.8)
Gentamicin	8	0.0 (0.0, 40.2)	39	0.0 (0.0, 11.2)	14	35.7 (14.0, 64.4)	32	12.5 (4.1, 29.9)
Ofloxacin	8	50.0 (17.4, 82.6)	39	66.7 (49.7, 80.4)	14	64.3 (35.6, 86.0)	32	62.5 (43.7, 78.3)
Oxacillin	8	50.0 (17.4, 82.6)	39	64.1 (47.2, 78.3)	14	85.7 (56.2, 97.5)	61	82.0 (69.6, 90.2)
Rifampicin	6	0.0 (0.0, 48.3)	36	5.6 (1.0, 20.0)	13	0.0 (0.0, 28.3)	32	0.0 (0.0, 13.3)
Tobramycin	6	16.7 (0.9, 63.5)	36	33.3 (19.1, 51.1)	13	53.9 (26.1, 79.6)	32	15.6 (5.9, 33.5)
Vancomycin	8	0.0 (0.0, 40.2)	38	0.0 (0.0, 11.4)	14	0.0 (0.0, 26.8)	32	0.0 (0.0, 13.3)

When cases of MRSA were detected, a screening program was applied in addition to standard precautions including alcohol hand rub. In contrast to the UK study mentioned above[12], Lucet et al also isolated patients directly on admission to ICU in a preventive manner when MRSA-carriage was suspected[14]. This was continued until negative screening results were obtained, which seems to be important for the prevention of early cross-transmission. Rapid genetic methods for MRSA-detection enable the time from screening to detection to be reduced, and isolation facilities can be used more efficiently[15, 16]. When there is an epidemic or endemic spread of multidrug resistant bacteria and the threshold for losing control over the outbreaks has been passed it may be difficult or impossible to reverse the resistance problem in a short perspective. In this situation, when isolation facilities are not available for all patients that need it, the compliance to basic hygienic rules is even more important.

Data collected from January 1997 through June 2003 from ICUs registered with the Krankenhaus Infektions Surveillance System (KISS) in Germany identified treatment in a medical or surgical ICU and infection with methicillin-resistant *S. aureus* or multidrug-resistant *P. aeruginosa* as independent determinants of death from nosocomial pneumonia and methicillin-resistant *S. aureus* as the causative agent associated with increased mortality from primary blood stream infection[17]. *S. aureus* is a common cause of ventilator-associated pneumonia (VAP). VAP due to MRSA is associated with increased overall length of stay (LOS) and also ICU LOS when compared with MSSA-related VAP[18].

For *A. baumannii*, the median resistant rate for imipenem in Care-ICU was 11.7% and the highest result was reported by the ICU in Malta with more than 90% resistant. In a study conducted in Italy covering 45 hospitals[19], *A. baumannii* was common among all studied Italian ICU and showed a high level of resistance to all the antibiotics tested including imipenem (58%). Resistance rates are high in the Mediterranean region when compared to northern Europe. Data from Care-ICU show that Turkey has 41.5% of *A. baumannii* isolates from ICU being resistant to imipenem compared to 0% in Sweden and Estonia. Risk factors associated with Carbapenem-resistant *A. baumannii* (CR-AB) acquisition include ICU-wide variables, such as the prevalence of ICU colonized patients and ICU antibiotic use over the preceding three months, as well as patient-related variables[20]. Among colonized patients, risk factors for CR-AB infection include transfusion and the proportion of body sites colonized with CR-AB. CR-AB infection is independently associated with increased hospital mortality and prolonged ICU stay. Multidrug-resistant *A. baumannii* (MDR-AB) has emerged as an increasingly problematic cause of hospital-acquired infections in the ICU and is resistant to most standard antimicrobials but often retains susceptibility to polymyxin B and doxycycline[5]. A range of infection control measures, aiming at reducing environmental contamination with the resistant strain, include use of a closed tracheal suction system for all patients receiving mechanical ventilation, use of nebulized colistin for patients with evidence of mild to moderate ventilator-associated pneumonia, improved availability of alcohol for hand decontamination, and clearer designation of responsibilities and strategies for cleaning equipment and the environment in the proximity of patients colonized or infected with MDR-AB[21]. In our ICU, closed suction system to reduce dispersion in the environment is done when there is a positive result of a MDR organism isolated from sputum culture. Stephens and colleagues reported that the number of new isolates in an acute care hospital decreased by dedicating an infection control professional to critical care, daily surveillance, isolation of positive MDR-AB patients, universal gloving, and routinely reporting results[22].

In the Care-ICU study, the median resistant rates for ceftazidime and imipenem for *P. aeruginosa* were 11.0% and 21.6 % respectively. The highest values were reported by the ICUs in Turkey, while for Malta, we were among the lowest for ceftazidime resistance and slightly above median for imipenem resistance. In a multi-centre study in Turkey, 51.1% of *P. aeruginosa* isolates were resistant to fluoroquinolones, 50.7% to ceftazidime, 38.7% to imipenem, and 30.0% to piperacilin-tazobactam [8]. Brahmi and co-workers studied the effect of reducing ceftazidime use in an ICU upon Gram-negative bacterial resistance, particularly as regards *P. aeruginosa* and concluded that restriction of ceftazidime use was efficient in reducing antimicrobial resistance [23]. On the other hand, Combes and colleagues investigated the impact of piperacillin resistance on the outcomes of *P. aeruginosa* VAP for patients who had received appropriate empiric antibiotics and found that piperacillin resistance was associated with increased disease severity at VAP onset[24].

Conclusion

The very high frequencies of antibiotic resistance among *S. aureus*, *P. aeruginosa* and *A. baumannii* isolated from patients admitted to Malta ICU is of concern. There is an urgent need for increased compliance to hygiene rules and improved infection control and the most efficient infection control interventions have to be defined. Feedback on antimicrobial resistance is a necessary tool to start actions against emergence of antibiotic resistance, misuse of antibiotics and low compliance to hygienic precautions.

Acknowledgements

Thanks to Hans Gill for excellent statistical support. CARE-ICU is funded by the EU Commission (DG SANCO) sponsored IPSE-project (http://ipse.University-lyon1.fr) and STRAMA (www.strama.org), Smittskyddsinstitutet (www.smittskyddsinstitutet.se).

References

1. Merz LR, Warren DK, Kollef MH, Fridkin SK, Fraser VJ. The impact of an antibiotic cycling program on empirical therapy for gram-negative infections. *Chest*. 2006 Dec;130(6):1672-8.

2. Fridkin SK, Hill HA, Volkova NV, Edwards JR, Lawton RM, Gaynes RP, McGowan JE Jr; Intensive Care Antimicrobial Resistance Epidemiology Project Hospitals. Temporal changes in prevalence of antimicrobial resistance in 23 US hospitals. *Emerg Infect Dis*. 2002 Jul;8(7):697-701.

3. Huang SS, Yokoe DS, Hinrichsen VL, Spurchise LS, Datta R, Miroshnik I, Platt R. Impact of routine intensive care unit surveillance cultures and resultant barrier precautions on hospital-wide methicillin-resistant *Staphylococcus aureus* bacteremia. *Clin Infect Dis*. 2006 Oct 15;43(8):971-8.

4. Cosgrove SE, Sakoulas G, Perencevich EN, Schwaber MJ, Karchmer AW, Carmeli Y. Comparison of mortality associated with methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* bacteremia: a meta-analysis. *Clin Infect Dis*. 2003 Jan 1;36(1):53-9.

5. Holloway KP, Rouphael NG, Wells JB, King MD, Blumberg HM. Polymyxin B and doxycycline use in patients with multidrug-resistant *Acinetobacter baumannii* infections in the intensive care unit. *Ann Pharmacother*. 2006 Nov;40(11):1939-45.

6. Davis KA. Ventilator-associated pneumonia: a review. J Intensive Care Med. 2006 Jul-Aug;21(4):211-26.

7. Suetens C, Ramboer I, Morales I, Wilson J, Hanberger H. Improving patient safety in Europe – Latest results of the IPSE surveillance network. Poster in the 17th European Congress of Clinical Microbiology and Infectious Diseases (2007). Available from URL: http://helics.univ-lyon1.fr/Working%20packages/WP5/Poster_Surveillance_final.pdf (last accessed 14th September 2007).

8. Leblebicioglu H, Rosenthal VD, Arikan OA, Ozgültekin A, Yalcin AN, Koksal I, Usluer G, Sardan YC, Ulusoy S; Turkish Branch of INICC. Device-associated hospital-acquired infection rates in Turkish intensive care units. Findings of the International Nosocomial Infection Control Consortium (INICC). *J Hosp Infect*. 2007 Mar;65(3):251-7.

9. Bracco D, Dubois MJ, Bouali R, Eggimann P. Single rooms may help to prevent nosocomial bloodstream infection and cross-transmission of methicillin-resistant *Staphylococcus aureus* in intensive care units. *Intensive Care Med*. 2007 May;33(5):836-40.

10. Mikolajczyk RT, Sagel U, Bornemann R, Krämer A, Kretzschmar M. A statistical method for estimating the proportion of cases resulting from cross-transmission of multi-resistant pathogens in an intensive care unit. *J Hosp Infect*. 2007 Feb;65(2):49-55.

11. Goldmann DA, Weinstein RA, Wenzel RP, Tablan OC, Duma RJ, Gaynes RP, Schlosser J, Martone WJ. Strategies to Prevent and Control the Emergence and Spread of Antimicrobial-Resistant Microorganisms in Hospitals. A challenge to hospital leadership. *JAMA* 1996;275:234-40.

12. Cepeda JA, Whitehouse T, Cooper B, Hails J, Jones K, Kwaku F, et al. Isolation of patients in single rooms or cohorts to reduce spread of MRSA in intensive-care units: prospective two-centre study. *Lancet* 2005;365:295-304.

13. Björholt I, Haglind E. Cost-savings achieved by eradication of epidemic methicillin- resistant *Staphylococcus aureus* (EMRSA)-16 from a large teaching hospital. *Eur J Clin Microbiol Infect Dis* 2004;23:688-695.

14. Lucet J-C, Paoletti X, Lolom I, Paugam.Burtz C, Trouillet J-L, Timsit J-F, Deblangy C, Andremont A, Regnier B. Successful long-term program for controlling methicillin-resistant *Staphylococcus aureus* in intensive care units. *Intensive Care Med*. 2005;31:1051-7

15. Francois P, Koessler T, Huyghe A, Harbarth S, Bento M, Lew D, Etienne J, Pittet D, Schrenzel J. Rapid *Staphylococcus aureus* agr type determination by a novel multiplex real-time quantitative PCR assay. *J Clin Microbiol*. 2006;44:1892-5.

16. Struelens MJ, Denis O. Rapid molecular detection of methicillin-resistant *Staphylococcus aureus*: a cost-effective tool for infection control in critical care? *Crit Care*. 2006;10:128

17. Gastmeier P, Sohr D, Geffers C, Behnke M, Rüden H. Risk factors for death due to nosocomial infection in intensive care unit patients: findings from the Krankenhaus Infektions Surveillance System. Infect Control Hosp Epidemiol. 2007 Apr;28(4):466-72.

18. Shorr AF, Tabak YP, Gupta V, Johannes RS, Liu LZ, Kollef MH. Morbidity and cost burden of methicillin-resistant *Staphylococcus aureus* in early onset ventilator-associated pneumonia. Crit Care. 2006;10(3):R97.

19. Nicoletti G, Schito G, Fadda G, Boros S, Nicolosi D, Marchese A, Spanu T, Pantosti A, Monaco M, Rezza G, Cassone A, Garaci E; CIGAR (Gruppo Cooperativo Infezioni Gravi ed Antibiotico Resistenza). Bacterial isolates from severe infections and their antibiotic susceptibility patterns in Italy: a nationwide study in the hospital setting. J Chemother. 2006 Dec;18(6):589-602.

20. Playford EG, Craig JC, Iredell JR. Carbapenem-resistant *Acinetobacter baumannii* in intensive care unit patients: risk factors for acquisition, infection and their consequences. *J Hosp Infect*. 2007 Mar;65(3):204-11.

21. Wilks M, Wilson A, Warwick S, Price E, Kennedy D,

Ely A, Millar MR. Control of an outbreak of multidrug-resistant *Acinetobacter baumannii*-calcoaceticus colonization and infection in an intensive care unit (ICU) without closing the ICU or placing patients in isolation. *Infect Control Hosp Epidemiol*. 2006 Jul;27(7):654-8.

22. Stephens C, Francis SJ, Abell V, DiPersio JR, Wells P. Emergence of resistant *Acinetobacter baumannii* in critically ill patients within an acute care teaching hospital and a long-term acute care hospital. *Am J Infect Control*. 2007 May;35(4):212-5.

23. Brahmi N, Blel Y, Kouraichi N, Lahdhiri S, Thabet H, Hedhili A, Amamou M. Impact of ceftazidime restriction on gram-negative bacterial resistance in an intensive care unit. *J Infect Chemother*. 2006 Aug;12(4):190-4.

24. Combes A, Luyt CE, Fagon JY, Wolff M, Trouillet JL, Chastre J. Impact of piperacillin resistance on the outcome of *Pseudomonas* ventilator-associated pneumonia. *Intensive Care Med*. 2006 Dec;32(12):1970-8.