Original article

Impact of Antibiotic Policy in a Tertiary Care Research Institute Hospital in Egypt: Three Years Experience

Hala Badawi [1,2], Manal Saad Diab[1] and Manal El Said [1, 2]

[1]Microbiology Department, [2]Infection Control Unit, Theodor Bilharz Research Institute (TBRI)
Giza, Egypt

Introduction

The main forces driving the increase in antimicrobial-resistant bacteria are poor infection control practices and inappropriate use of antibiotics. Once these factors are addressed, specific antibiotic utilization strategies may help decrease or prevent the emergence of resistance. These strategies include antibiotic restriction, combination therapy, and antibiotic cycling. [1]

Dependence on one class of antibiotic to treat a population, despite optimal dosing and duration of treatment, may allow for the selection of resistant organisms within that population. Cycling, or rotating antibiotics within or between classes, by altering the selective pressure for bacteria to develop resistance to any particular antibiotic, may be an important component, from a population perspective, of antimicrobial stewardship.[1]

An antibiogram is particularly helpful for choosing empiric and pathogen-directed treatment regimens. It also assists in antibiotic "streamlining", the process by which excessively broad-spectrum empiric antibiotic therapy can be switched to narrower spectrum therapy aimed only at the implicated pathogen(s).

It must be acknowledged that an antibiogram-based guideline does not have an unlimited duration of utility. It is likely that shifts in antibiotic usage engendered by the creation of the guideline will, over time, lead to a change in resistance patterns. Thus, it is prudent to update antibiograms and antibiogram-based antibiotic guidelines on a regular basis.[2]

Antibiotic cycling involves the deliberate removal of the antimicrobial of choice to treat a particular infectious syndrome in a specific unit with the intention of reintroducing that antimicrobial at a predetermined time in the future. Several antibiotics are commonly rotated in this fashion. Cycling takes advantage of the observation that resistance to a particular antimicrobial decreases when that antimicrobial is no longer used. In addition to restriction, antibiotics are rotated to maintain or promote antibiotic heterogeneity in order to alter the selective pressures present and thus prevent the emergence of resistance to any particular antibiotic.[1]

Community prescribing practices have been shown to influence rates of resistance in common bacterial pathogens, and long-term–care facilities are increasingly being recognized as reservoirs for antibiotic-resistant pathogens.[3]

Antimicrobial resistance in *S. aureus* emerged soon after penicillin came into common use in the 1940s. During the next two decades, resistance of this pathogen to penicillin became widespread, followed by increasing resistance to the new semisynthetic penicillinase-resistant antimicrobial drugs (e.g., methicillin, oxacillin, nafcillin). In the last 20 years, methicillin-resistant *S. aureus* (MRSA) has spread throughout the world in healthcare settings. In addition, serious MRSA infection has been

Corresponding author:
Hala Badawi, Theodor Bilharz Research Institute (TBRI), Giza, Egypt
Email: halabadawi2@yahoo.com

increasingly reported in persons without identified pre-disposing risk, including recent healthcare exposure. [4]

Members of the family Enterobacteriaceae producing beta-latamases constitute a serious threat to current beta-lactam therapy.[5] In addition, guidelines of the National Committee for Clinical Laboratory Standard (NCCLS)[6] suggest that confirmed extended spectrum beta-lactamase (ESBL) producing strains should be reported as resistant to all penicillins, cephalosporins and aztreonam.

MRSA and ESBL infections have been increasing at an alarming rate world-wide over the past two decades. They are responsible for nosocomial infections and adverse patient outcomes.[7] Numerous reports describe nosocomial outbreaks in various countries.[8,9]

These infections may be life-threatening and cause considerable morbidity as they are of special concern for several reasons. They are associated with prolonged hospitalization and increased costs with few therapeutic options. These multidrug-resistant bacteria (MRB) increasingly have spread from hospital settings to noninstitutional environments.[8] On the other hand, prolonged MRSA carriage was found to occur after hospital discharge increasing the infection by this organism in both community and hospital settings.[10] Transmission of such infections occurs primarily from colonized or infected patients to other patients or staff and vice versa mainly through transiently-colonized hands of healthcare personnel. The environment also contributes to such transmission.[10,11]

In our institute hospital, a surveillance study in 2004 showed that MRSA and ESBL represented 11.9% and 29.9% of nosocomial infections respectively.[12] This triggered us to implement an antibiotic policy with cycling and follow up.

Objectives
The aim of implementing an antibiotic policy in Theodor Bilharz Research Institute (TBRI) Hospital is to offer guidelines for the rational use of antimicrobial agents by promoting best practice in: Prophylactic therapy, Empirical therapy and Definitive therapy in an attempt to retard the emergence and spread of resistance.

Population and Methods
Site of the study
TBRI hospital is a tertiary care hospital with 300 beds. Antibiotic policy was implemented as a part of IC program in 2005. All departments of the TBRI Hospital were included; urosurgery, general surgery, tropical medicine, nephrology, intensive care unit and economic section.

The microbiology laboratory staff of TBRI is authorized

to isolate, identify and to test the sensitivity to antibiotics of the bacteria of the surveillance plan under protocol. The laboratory records the pathological samples, cultures the samples according to standard protocols, identifies the bacteria to be studied (family, kind, species and eventually serotype), performs standard antibiogram and complementary tests, respecting the NCCLS norms, and interprets the results according to the current norms and context (nosocomial infection, colonization or another sort of infection).

Study Population
All patients hospitalized during the period of study were included and outpatients were excluded.

The included samples:[13] All samples for diagnostic purposes were included. Excluded were duplicates: an isolate from a patient for whom a strain of the same species and same antibiotype had already been taken during the same period.

The included strains: All bacterial isolates including: MRSA and ESBL-producing enterobacteria.

Data Collection
Data were collected by members of the infection control unit of TBRI from January 1, 2005 to May 31, 2005 on three checklist forms. The data were obtained from clinical records: Laboratory data (bacteriological results, complementary examinations), medical charts, temperature charts, antibiotic and operation room records.

The administrative data: The number of beds, the number of direct admissions and the number of full days hospitalization (>24h) in different departments during the period of study.

Data from the laboratory (first part on laboratory form, second part on MRB form): The total number of identified strains (sensitive S, intermediate I and resistant R), after elimination of duplicates. For each MRB, a form was filled in with the following information: hospital stay identification, age, gender, date of sample (first positive diagnostic sample during the period), the department's specialty, site of sample, the microorganism concerned. If the MRB isolated was a MRSA, its sensitivity to vancomycin was investigated. If the MRB isolated was enterobacteria, the possibility of being ESBL was investigated.

Data from the hospital (Antibiotic usage surveillance form):
Data on Surgical procedure including: Date of surgical intervention, NNIS (National Nosocomial Infections Surveillance system, CDC, Atlanta). procedure category, hair removal and its method, showering, ASA (American Society of Anesthesiologists) score, duration of surgery, wound class, elective or emergency, endoscopic surgery,

trauma, multiple procedure, implant of prosthesis, drainage and its method, date of discharge and date of follow up visit.

Description of antibiotic: time of administration, type of antibiotic, duration, indication (specific, empirical or a surgical prophylaxis) and the main diagnosis.

Organization of the study:
First: A surveillance study was done including developing overall infection rates as well as identifying the most commonly encountered MRB microorganisms.

Second: A study of the antibiotics used for prophylaxis, empiric treatment and therapy from January 1, 2005 to May 31, 2005 was done using a well-designed form for data collection:

Third: Data analysis was done and an antibiotic policy was proposed.

Fourth: One year duration (July 1, 2005 – July 1, 2006; July 1, 2006 – April 1, 2007) was given for follow up and evaluation of the new policy.

Fifth: Cycling of antibiotics was done accordingly. Restoration of results and feedback was obtained through final written reports at the end of the study. These reports were sent to bacteriology laboratory, administration, and different departments.

Data analysis:
The capture and analysis of the data was done by using the Epi Info version 6 software.

Judgment criteria:
The percentage of MRB (MRSA and ESBL) within the bacterial species.

The attack rate of MRB for 100 admissions: the number of MRB carrier patients in relation to the number of admitted patients during the period of the study.

The incidence rate of MRB carrier patients, for 1000 days of hospitalization: the number of MRB carrier patients in relation to the number of hospitalization days during the study period.

Results:
Surveillance study:
Nosocomial infection (NI): Hospital infection was controlled so that the infection rate was lowered from 5.8% in 2004 to 2.7% in 2007 (P<0.0001).

Frequency distribution of NI among different hospital departments: Regarding the urosurgery and general surgery departments, the infection rate was lowered from

44.8%, 32.8% in 2004 to 38% and 6.3% in 2007 respectively with highly statistically significant difference for general surgery department (P <0.0001). On the other hand, there was a rising infection rate in nephrology and tropical departments. In fact, this situation is also true for
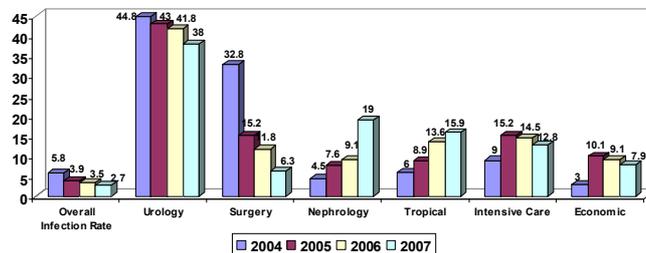

Figure 1: Comparison of nosocomial infection rates in different hospital departments in four consecutive annual periods

the ICU and economic section during the period from 2004 to 2005. After that, the infection rate in the ICU and economic sections was lowered from 15.2%, 10.1% in 2005 to 12.8% and 7.9% in 2007 respectively (Figure 1).

The prevalence of MRB (Figure 2): The prevalence of MRSA was lowered from 11.9% in 2004 to 1.6% in 2007 (P<0.02), while the prevalence of ESBL was 29.9% in 2004 compared to 12.6% in 2007 (P<0.01). MRSA species represented 80% of *Staphylococcus aureus* isolates in 2004 compared to only 5% in 2007 (P<0.0001). ESBLs represented 37.7% of enterobacterial isolates in 2004 compared to 14% in 2007 (P<0.004). The attack rate was 2.4% in 2004 and 0.39% in 2007 and the incidence rate was lowered from 2.8% in 2004 to 0.4% in 2007 (Table 1).

Table 1: Attack and Incidence Rates of Multi-Resistant Bacteria

Year	No. of admitted patients	No. of MRB	No. of total hospitalization days	Attack Rate	Incidence rate
2004	1162	28	10124	2.4	2.8
2005	2021	20	17541	0.9	1.1
2006	3099	26	28124	0.8	0.9
2007	2291	9	21688	0.39	0.4

Antibiotic policy:
Cycling of antibiotic policy (Table 2):
Upon studying the antibiotics used for prophylaxis from January 1, 2005 to May 31, 2005, the outstanding feature was that efficacy of cefazolin was 74%-85% before implementation of the policy (2005) and became 34%-50% in 2006. Also, ampicillin-sulbactam efficacy was 67%-75%, 7%-11% before and after implementation respectively.

So, cycling of antibiotic policy in 2006 to cefaclor (efficacy 60%-80%) and augmentin (efficacy 79%-85%)

was implemented. Consequently, in 2007 their efficacies diminished to 19%-27.3%, 17%-35% for both drugs respectively.

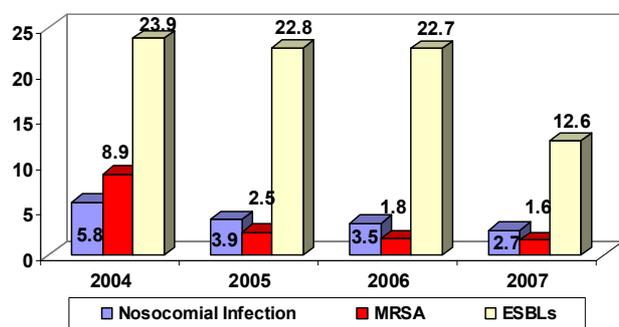Once again, cycling of antibiotic policy in 2007 to cefa-

Figure 2: Frequency distribution of Multi-Resistant Bacteria in four consecutive annual periods

zolin regained its efficacy (50%-100%) and gentamicin (efficacy 48%-85.7%) was implemented. This policy has to be followed up from January 1-May 31, 2008 to guide further cycling of the policy. Before implementation of policy in 2005, efficacy of gentamicin was as low as 14% and that of amikacin 42%, while that of tobramycin was 76.6% which was then included in cycle 1 (2005). Then, the sensitivity of amikacin was regained in 2006 (80%-100%) and that of gentamicin in 2007 (48%-85.7%). Table 2 illustrates cycling for empirical and specific therapy on the basis of antibiotic efficacy evaluation.

Feedback (Figure 3):

The implementation of an antibiotic policy reflected greatly on decreasing the post-operative need for antibiotherapy and consequently duration of hospitalization was significantly lowered from 14.5% in 2004 to 6.3% in 2007 (P<0.0001). Hospital re-admission was diminished from 12.6% in 2004 to 4.9% in 2007 (P<0.0001). Mortal-

Table 2: Cycling of Antibiotic Policy in three consecutive annual periods

Type of Antibiotic Therapy	Antibiotic Policy							
	Cycle 1 (1/7/2005)			Cycle 11 (1/7/2006)			Cycle 111 (1/7/2007)	
	*Selected Antibiotics	Efficacy (%)		Selected Antibiotics	Efficacy (%)		Selected Antibiotics	Efficacy (%)
		Before (1/1/-31/5/2005)	After (1/1/-31/5/2006)		Before (1/1/-31/5/2006)	After (1/1/-31/5/2007)		Before (1/1/-31/5/2007)
Prophylactic								
Clean	Cefazolin	74-85	34-50	Cefaclor	60-80	19-27.3	Cefazolin	50-100
Clean-Contaminated	Ampicillin-sulbactam	67-75	7-11	Augmentin	79-85	17-35	Gentamycin	48-85.7
Empirical								
Urine	Ciprofloxacin	82	27.3	Ceftriaxone	60	38.3	Tazocin	62.5
Sputum	Ampicillin-sulbactam	86	18.2	Ceftriaxone Clindamycin	100 100	40 42.8	Amikacin	79.1
Wound	Ampicillin-sulbactam	75	23.5	Clindamycin	50	50	Amikacin	75
Blood	Ciprofloxacin	79	37.5	Clindamycin	64.3	47.3	Amikacin	68
Ascitic fluid	Ampicillin-sulbactam	66.7	34.3	Clindamycin	100	0	Amikacin	100
Specific								
MRSA	Clindamycin	70	20	Amikacin	80	59	Aztreonam	100
ESBL	Tazocin	76.6	54	Tobramycin	100	92	Amikacin	92
Gram –ve	Ciprofloxacin	69	11	Amikacin	86	80	Amikacin	80
Gram +ve	Ampicillin-sulbactam	88	55	Augmentin	83	56.3	Cefazolin	100

* In 2005: Gentamicin efficacy = 14%, Tobramycin efficacy= 22%, Amikacin efficacy= 42%

ity rate due to infection was lowered from 0.95% in 2004 to 0.17% in 2007 (P<0.001).

Duration of treatment courses was accordant in 20% in 2005 compared to 65% in 2007 (P< 0.0001) (Figure 4).
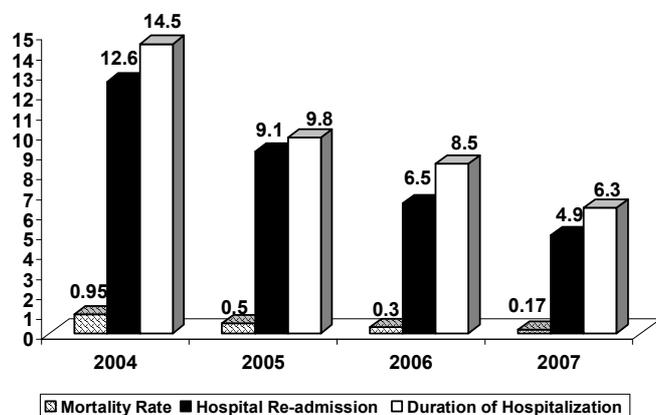

Figure 3: Feedback of Implementation of Antibiotic Policy

Discussion

Nosocomial infections (NIs) represent a major problem in health care facilities, resulting in extended duration of
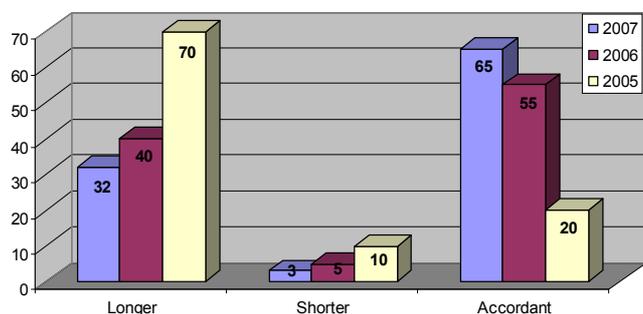

Figure 4: Comparison of Antibiotic Prescription with Guidelines

care, substantial morbidity and mortality and excess costs.[14] NIs constitute one of the greatest challenges of modern medicine and their socio-economic costs are continually rising. The focus for reducing the incidence of NIs should be on maintaining a microbiologically safe environment.[15, 16]

The nosocomial infection rate in this study was significantly lowered from 5.8% in 2004 to 2.7% in 2007. This was accomplished by adequate infection control practice which is one of the key components for limiting spread of nosocomial infections.[17] These precautions include handwashing, routine use of gloves, cleaning and disinfection of the environmental surfaces[18] and the application of antibiotic policy from 2005 to 2007.

Although infection control policies are unlikely to prevent resistance from emerging, they are essential to

decrease the spread of antimicrobial-resistant bacteria. Handwashing is the most important infection control method. It prevents infections by decreasing the contamination of medical devices when they are manipulated and by preventing person-to-person transmission of potentially virulent or resistant organisms.[1] Optimizing infection control practices through inexpensive educational interventions has been shown to decrease rates of NI.[19] Infection control policies can help prevent the horizontal transmission of resistant bacteria through early identification and proper isolation practices. This preventive action can also decrease infection rates, since colonization is a known precursor to infections caused by resistant bacteria.[20]

There was a significant decrease of the infection rate in the general surgery department from 32.8% in 2004 to 6.3% in 2007. This was attributed to the establishment of a new central sterilization unit in the hospital through the efforts of members of the infection control unit. On the other hand, there was a rising infection rate in nephrology and tropical departments proportional to increased samples sent to the microbiology laboratory following the advice of infection control officers. The tremendous rise of infection in these departments in 2007 was attributed to new construction in these units. The infection rate in the ICU and economic sections was also increasing during the period from 2004 to 2005, also due to increased microbiological sampling.
Then, the infection rate in ICU and economic section was lowered from 15.2%, 10.1% in 2005 to 12.8% and 7.9% in 2007 respectively with the application of infection control measures.

Antibiotic resistance in bacteria is a contemporary global public health problem.[21] The incidence of infections caused by MRB is increasing worldwide, and infections caused by resistant bacteria are associated with increased costs, morbidity, and mortality.[22] However, the main factors driving the increase in antimicrobial-resistant bacteria are the increased use of antimicrobials especially broad-spectrum ones.[1]

Accurate estimates of the incidence of MRSA infection are essential to determine effects on health and health-care expenditures.[23] The prevalence of MRSA and ESBL in our study was significantly lowered from 11.9% and 29.9% in 2004 to 1.6% and 12.6% in 2007 respectively. The incidence rate of MRB was lowered from 2.8% in 2004 to 0.4% in 2007 and the attack rate was 2.4% in 2004 and 0.39% in 2007. Similar rates of infection have been recorded in other studies.[23,24]

The first steps toward preventing or reducing the emergence of resistant pathogens are effective infection control policies. A second essential component is antimicrobial stewardship. Many studies have shown that as much as 50% of antimicrobial use is inappropriate. Excessive and inappropriate antimicrobial use results in

strong selective pressures that facilitate the emergence of antimicrobial-resistant pathogens. In addition to limiting the inappropriate use of antibiotics, antimicrobial stewardship involves optimizing the selection, dosage, and duration of antimicrobial therapy to prevent and treat infections.[25,26]

Once antimicrobial stewardship has been optimized, potential antibiotic utilization strategies identified by national consensus guidelines can be developed including restriction of antibiotics, combination therapy, and antibiotic cycling. Antimicrobial stewardship attempts to control the leading factor associated with antimicrobial resistance: inappropriate use of antibiotics. Such use more often results from inadequate information than from inappropriate behavior.[26]

Our study demonstrates an increase in cefazolin and ampicillin-sulbactam resistance when they were used for prophylaxis (cycle 1). However, cefazolin regained its efficacy in cycle 3 when it was replaced in cycle 4 with cefaclor while ampicillin-sulbactam retained its resistance.

It must be acknowledged that an antibiogram-based guideline does not have an unlimited duration of utility. It is likely that shifts in antibiotic usage engendered by the creation of the guideline will, over time, lead to a change in resistance patterns. Thus, it is prudent to update antibiograms and antibiogram-based antibiotic guidelines on a regular basis. A yearly review should be regarded as a bare minimum. "Cycling" antibiograms, which are constantly updated, are probably optimal if an institution has the information technology resources to create them.[2] Cycle duration should be short in order to maintain the benefits associated with rapid cycling periods, but it should be long enough not to confuse and frustrate the prescribing practitioners. Studies performed more recently have used cycle durations of 1 to 4 months to achieve this balance, although the optimal duration is not known.[1]

This study demonstrates a decrease in gentamicin, tobramycin and amikacin resistance when they were restricted from all types of antibiotic therapy (cycle 1). Tobramycin resistance decreased once more without a concomitant increase in amikacin resistance (cycle 2). Gentamicin resistance decreased once more without a concomitant increase in amikacin resistance (cycle 3). These results were similar to that of Gerding[26] who found that the reintroduction of aminoglycosides was not associated with an increase in their resistance. Multiple studies demonstrated a decrease in gentamicin and tobramycin resistance when they were replaced by amikacin. Most available data on the potential benefits of cycling come from studies of aminoglycosides.[27]

Ciprofloxacin was replaced by ceftriaxone (cycle 4) as the empiric agent of choice for suspected Gram-negative

urinary tract infections. Patients were followed before and after the change in antibiotics. The change was associated with a decrease in infection rate. Similar results have been published from a cardiothoracic intensive care unit (ICU).[28]

Generally, after annual follow-up, there was a decrease in infections caused by antibiotic-resistant bacteria and consequently duration of hospitalization; hospital readmission and mortality associated with infection. This is probably a consequence of more effective empiric therapy resulting from the improved resistance profiles of the infecting organisms. So, our study showed that the cycling intervention may also have resulted in a decrease in the total number of nosocomial infections and in the rates of infections caused by resistant Gram-positive cocci and Gram-negative rods on ICU and non-ICU wards as well, which was in accordance with other studies.[29] Also, the duration of treatment courses was significantly accordant which reflects compliance with the protocol.

Conclusion and Recommendations

Our study provides evidence that cycling can be a successful strategy in stabilizing or decreasing resistance MRB. Cycle duration should be short in order to maintain the benefits associated with rapid cycling periods. Consequently, surveillance on the evolution of the resistance patterns and antibiotic consumption should be mandatory in each hospital. Collaboration between the clinicians, microbiologists, pharmacists and hygienists together and with the infection control officers should also be mandatory. Guideline development and implementation, formulary restrictions, and quality-improvement teams, are techniques that have been shown to have a positive effect on changing prescribing patterns. In the future we hope to apply computer-assisted prescribing in our institution after completion of the hospital intranet.

References

1. Dubberke ER, Fraser VJ. Cycling and Other Strategies to Slow and Reverse Antibiotic Resistance, Infect Med 2004*;* 21(11):544-556.
2. Paterson DL, Rice LB. Empirical antibiotic choice for the seriously ill patient: are minimization of selection of resistant organisms and maximization of individual outcome mutually exclusive? Clin Infect Dis 2003;36:1006-1012.
3. Chen DK, McGeer A, de Azavedo JC, Low DE. (1999): Decreased susceptibility of Streptococcus pneumoniae to fluoroquinolones in Canada. Canadian Bacterial Surveillance Network. N Engl J Med 1999; 341: 233-239.
4. Crum NF, Lee RU, Thornton SA et al. Fifteen-year study of the changing epidemiology of methicillin-resistant *Staphylococcus aureus*. Am J Med 2006 ; 119: 943-951.
5. Tumbarello M, Sanguinetti M, Montuori E et al. Predictors of mortality in patients with bloodstream infections caused by extended-spectrum-ß-lactamase-producing Enterobacteriaceae: importance of inadequate

initial antimicrobial treatment. Antimicrob Agents Chemother2007 ; 51:1987–1994.

6. National Committee for Clinical Laboratory Standards . Performance standards for antimicrobial susceptibility testing NCCLS approved standard M10-S9. National Committee for Clinical Laboratory Standards, Wayne, PA 1999.

7. Centers for Disease Control. Molecular Epidemiology of Methicillin-Resistant *Staphylococcus aureus*. Emerg Infect Dis 2001; 7(2) : 323-6.

8. Zhiming L, Willke RJ, Rittenhouse BE, et al. Comparison of Length of Hospital Stay for Patients With Known or Suspected Methicillin-Resistant Staphylococcus Species Infections Treated With Linezolid or Vancomycin: A Randomized, Multicenter Trial. Pharmacotherapy 2001; 21(3):263-274.

9. Fluit AC, Wielders CL, Verhoef J, Schmitz FJ . Epidemiology and Susceptibility of 3,051 *Staphylococcus aureus* Isolates from 25 University Hospitals Participating in the European SENTRY Study. J Clin Microbiol 2001; 39(10):3727-32.

10. Simor AE. Containing methicillin-resistant *S aureus*. Surveillance, control, and treatment methods. Postgrad Med 2001; 110(4):43-8; quiz.

11. Udo EE, AL-Obaid IA, Jacob LE, Chugh TD. Molecular characterization of epidemic ciprofloxacin- and methicillin- resistant *Staphylococcus aureus* strains colonizing patients in an intensive care unit. J Clin Microbiol 1996; 34(12):3242-44.

12. Badawi H, El-Said M. Detection of of Methicillin Resistant *Staphylococcus aureus* (MRSA) and Extended Spectrum β-Lactamases (ESBLs) among clinical isolates in Theodor Bilharz Research Institute Tertiary care hospital. 2004; unpublished data.

13. Berthelot Ph, Partier C, Muleer- Serieys C, Pean Y, Jarlier V. The methodological recommendations of the ONERBA scientific council for the surveillance of the resistance to antibiotics. 18th Anti- infectious Chemotherapy Interdisciplinary Meeting (RICAI). La Lettre de l`lnfectiologue 1999; XIV,3, 121-125

14. Hilburn J, Hammond BS, Fendler EJ, Groziak PA. Use of alcohol hand sanitizer as an infection control strategy in an acute care facility. Am J Infect Contr 2003; 31(2): 109-116.

15. Trampuz A and Widmer AF. Hand hygiene: a frequently missed lifesaving opportunity during patient care. Mayo Clin Proc 2004; 79(1): 109-116.

16. Cochrane J. Infection control audit of hand hygiene facilities. Nurs Stand 2003; 17(18): 33-38.

17. Lankford MG, Zembower TR, Trick E et al. Influence of role models and hospital design on hand hygiene of health care workers. Emerg Infect Dis 2003; 9 (2): 217-223.

18. Tokars JI, Arduino MJ, Alter MJ. Infection control in hemodialysis units. Infect Dis Clin North Am 2001; 15 (3): 797-812.

19. O'Grady NP, Alexander M, Dellinger EP et al. (2002): Guidelines for the prevention of intravascular catheter-related infections. Infect Contr Hosp Epidemiol 2002; 23:759-769.

20. Warren DK, Fraser VJ. Infection control measures to limit antimicrobial resistance. Crit Care Med 2001; 29(4 suppl): N128-N134.

21. Wright GD. The antibiotic resistome: the nexus of chemical and genetic diversity. Nat Rev Microbiol 2007 ;5: 175-186.

22. National Nosocomial Infections Surveillance (NNIS) System Report. Data summary from January 1992 through June 2003, issued August 2003. Am J Infect Contr 2003; 31: 481-498.

23. Kuehnert MJ, Hill HA, Kupronis BA et al. Methicillin-resistant–*Staphylococcus aureus* Hospitalizations, United States. Emerg Infect Dis 2005*;* 11(6): 868-872

24. El Kholy A, Baseem H, Hall GS, Procop GW, Longworth D L. (2003): Antimicrobial resistance in Cairo, Egypt 1999–2000: a survey of five hospitals. J Antimicrob Chemother 2003; 51, 625–630

25. Lieberman JM. Appropriate antibiotic use and why it is important: the challenges of bacterial resistance. Pediatr Infect Dis J 2003; 22: 1143-1151.

26. Dellit TH, Owens RC, McGowan JE et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin Infect Dis 2007 ; 44: 159–177.

27. Gerding DN. Antimicrobial cycling: lessons learned from the aminoglycoside experience. Infect Contr Hosp Epidemiol 2000; 21(1 suppl): S12-S17.

28. Kollef MH, Vlasnik J, Sharpless L et al. Scheduled change of antibiotic classes: a strategy to decrease the incidence of ventilator-associated pneumonia. Am J Respir Crit Care Med 1997; 156 (4 pt 1):1040-1048.

29. Hughes MG, Evans HL, Chong TW et al. Effect of an intensive care unit rotating empiric antibiotic schedule on the development of hospital-acquired infections on the non-intensive care unit ward. Crit Care Med 2004; 32: 53-60.