ANTIBIOTICS QUANTITY-BASED *Escherichia coli* RESISTANCE PATTERN IN PATIENTS AT SURGICAL AND PSYCHIATRIC WARDS, DR SOETOMO HOSPITAL, SURABAYA

Rebekah Juniati Setiabudi, Kuntaman, Iva Puspitasari
Department of Clinical Microbiology
Faculty of Medicine, Airlangga University

ABSTRAK

Penggunaan antibiotik adalah penyebab tersering resistensi mikroorganisme melalui selective pressure.3 Individu penerima dosis terapi antibiotik akan mengalami perubahan populasi mikroba flora normal. Resistensi antibiotik terhadap bakteri gram positif maupun gram negatif semakin meningkat di seluruh dunia. Penelitian ini ditujukan untuk mengetahui pengaruh kuantitas penggunaan antibiotik terhadap resistensi mikroflora normal usus pasien di ruang rawat inap psikiatri dan bedah, Dr. Soetomo Hospital Surabaya. Penelitian ini bersifat analitik observasional dengan rancang bangun potong lintang.Penelitian dilakukan dari bulan April sampai Juli 2010. Populasi adalah semua usap rektal pasien dewasa yang keluar rumah sakit dari ruang perawatan intensif dan ruang perawatan psikiatri di RSUD.Dr. Soetomo Surabaya. Pada penelitian ini sampel diambil dengan metode consecutive sampling. Kami mengidentifikasi mikroflora intestinal dengan medium selektif differensial McConkey, dilanjutkan uji biokimia IMVIC, dan uji sensitifitas mikroflora intestinal dengan metode difusi cakram antibiotik pada medium Muller Hinton. Antibiotika yang diuji yaitu seftriakson, sefotaksim, meropenem amikasin, tetrasiklin, ampisilin dan siprofloksasin, menunjukkan sensitifitas yang tinggi dari kisaran 64,4% sampai 100%. Perhitungan menunjukkan perbandingan resistensi yang sangat bermakna pada obat yang diujikan pada angka p= 0.000 sampai 0,008. Pola resisten mikroflora intestinal di ruang rawat inap bedah terhadap sefotaksim, seftriakson, ampisilin, tetrasiklin dan siprofloksasin berturut-turut sebesar 75%, 70%, 97,5%, 82,5% dan 70%, sedangkan yang sensitif terhadap amiksin dan meropenem berturut-turut sebesar 67,5% dan 100%. Kuantitas penggunaan antibiotika tertinggi adalah seftriakson sebesar DDD 362g dengan DDD/100 pasien hari adalah 31,2069 dari sejumlah 40 pasien. ***(FMI 2014;50:104-109)***

Kata kunci:*Escherichia coli, resistensi, antibiotika, sefotaksim, seftriakson, ampisilin, tetrasiklin, siprofloksasin, amiksin, meropenem*

ABSTRACT

The use of antibiotics is the most common cause of resistance of microorganisms through selective receiver pressure. Individuals dose antibiotic therapy will change the normal microbial flora populations. Antibiotic resistance against gram positive and gram negative is proliferating around the world. This study aimed to determine the effect of antibiotic use on resistance quantity of normal intestinal microflora of patients in psychiatric inpatient wards and surgery, Hospital Dr. Soetomo. This study was an observational analytic cross-sectional design. The study was conducted from April to July 2010. Population is all adult patients whose rectal swab out of a hospital intensive care and psychiatric care spaces in RSUD.Dr. Soetomo. In this study, samples were taken with consecutive sampling method. We identify the intestinal microflora with selective differential medium McConkey, followed IMViC biochemical tests, and test the sensitivity of the intestinal microflora by antibiotic disc diffusion method on Muller Hinton medium. Antibiotics were tested, namely ceftriaxone, cefotaxime, meropenem amikacin, tetracycline, ampicillin and ciprofloxacin, showed a high sensitivity of the range of 64.4% to 100%. Calculations show that a very significant proportion of resistance to the drug being tested on the numbers p=0.000 to 0.008. Resistance patterns of intestinal microflora in surgical inpatient unit to cefotaxime, ceftriaxone, ampicillin, tetracycline and ciprofloxacin, respectively for 75%, 70%, 97.5%, 82.5% and 70%, while sensitive and meropenem respectively amiksin - contributed by 67.5% and 100%. Quantity is the highest use of antibiotics ceftriaxone for DDD 362g with DDD/100 patient day is 31.2069 of the number of 40 patients. ***(FMI 2014;50:104-109)***

Keywords:*Escherichia coli, resistance, antibiotics, cefotaxim, sefotaksim, seftriakson, ampisilin, tetrasiklin, siprofloksasin, amiksin, meropenem*

Correspondence: Rebekah Juniati Setiabudi, Department of Clinical Microbiology, Faculty of Medicine, Airlangga University

INTRODUCTION

The problem of antibiotic resistance is a problem faced by all health services in the world, especially in developing countries, including Indonesia (Shears 2001, Okeke et al 2005). The use of antibiotics is the most common cause of resistance to microorganisms (Bronzwaer et al 2002, Farra et al 2002). The use of antibiotics contributes to antimicrobial resistance through selective pressure (Bronzwaer et al 2002). All

individuals who receive therapeutic doses of antibiotics will change the normal microbial flora populations, both in intestinal, respiratory and genitourinary tracts (Brunton et al 2005). Antibiotic resistance against gram positive and gram negative is increasing worldwide (Beekmann et al 2005, Erb et al 2007). In developing countries, about 44% to 97% of hospitalized patients received antibiotic prescription. This antibiotic is often prescribed unnecessarily or use improperly (Ansari 2001, Hu et al 2003). In the Far East, there are only very limited data publications, especially on clinical isolates of *Escherichia coli* resistance to antibiotics (Bell et al 2003, Kuntaman et al 2005, McDonald et al 2001, Hsueh et al 2002, Sheng et al 2002, Subekti et al 2003, Tjaniadi et al 2003). Data resistance in Indonesia are generally very limited in *Escherichia coli* as a pathogen that causes diarrheal diseases (Kuntaman et al 2005, Subekti et al 2003, Agtini et al 2005, Lesmana et al 2001, 2002). Study Group' Antimicrobial Resistance in Indonesia: Prevalence and Prevention' has conducted research carrier resistant bacteria with habitate in the rectum in the population on the island of Java. Rectal swab culture on individual and community hospitals showed microflora *Escherichia coli* as commensal intestinal bacteria and is often used as an indicator of antibiotic resistance in the population (Bruinsma et al 2003).

Based on research conducted by the previous Amrin (Antimicrobial Resistance in Indonesia-Netherlands) study group, it was found that from 3725 individuals (2494 in the community and 781 hospitalized individuals) 54% of *Escherichia coli* is a carrier that is resistant to antibiotics. In both of these populations, the use of antibiotics is an important factor in the emergence of antibiotic resistance (community with OR: 1.8; CI (95%) from 1.5 to 2.3, while in hospitalized individuals with OR : 2.5, CI (95%) 1.6 to 3.9 (Duerink et al 2007). Another study revealed dynamic microflora colonization and resistance of gram-negative aerobic bacteria in intestinal tract and oropharynx in the patients during and after treatment in the intensive care unit of a hospital (Filius et al 2005). Percentage of patients colonized with fecal microflora of *Escherichia coli* resistant to ampicillin and cephalothin showed a significant increase when the patient was out from the intensive care unit or hospital and did not change during the 3 months after hospital discharge. Frequency of this resistance will also significantly increase in patients with a longer hospitalization in an intensive care unit (Filius et al 2005).

In a study conducted in the Netherlands states that all combinations of normal intestinal microflora and combinations of antibiotics showed a higher prevalence of resistance in intensive care unit than in the non-intensive care (Filius et al 2005, NNIS System 2003, Archibald et al 1997). This can occur if the patient is treated longer in intensive care and more antibiotics are used (Alberti et al 2002). Indonesia has many pathogenic bacteria that are resistant to many classes of antibiotics (Tjaniadi et al 2003, Ieven et al 2003). Not much is known about the normal commensal flora resistance and the resistance of all properties in Indonesia (Duerink et al 2007). This study was aimed to determine the effect of the quantity of antibiotic use on the incidence of resistance of normal intestinal microflora of patients in psychiatric and surgical wards, Dr. Soetomo Hospital, Surabaya, Indonesia.

MATERIALS AND METHODS

This study was two-proportion difference test aimed to find differences in the quantity of antibiotic use on one risk factor, which was the effect of antibiotic resistance on intestinal microflora and the difference in quality to the quantity of antibiotics that may induce antibiotic resistance to intestinal microflora. Analysis results obtained will be useful to increase the use of antibiotics based on guidelines compliance, and can be used as a systematic reference in selecting standardized antibiotic consideration for the hospital. This study used observational analytic cross-sectional design.

This research was conducted in intensive care and psychiatric wards in Dr. Soetomo Hospital, Surabaya, from April to July 2010. Population affordable in this study was all adult patients whose rectal swab out of a hospital intensive care and psychiatric wards in Dr. Soetomo Hospital. In this study, samples were taken with consecutive sampling method, ie all study subjects are out of the hospital and met the inclusion criteria were included in the study from April to June 2011.

Inclusion criteria were all hospitalized patients from intensive care and psychiatric wards with a length of stay = 5 days, adults aged 21 years or married, and no diarrhea. Exclusion criteria were all patients who met the inclusion criteria but were not willing to participate in the study (not signed informed consent). Identification of intestinal microflora was done by differential selective medium McConkey, followed with IMViC biochemical tests. Intestinal microflora sensitivity test was performed with antibiotic disc diffusion method on Muller Hinton medium. We recorded a wide choice of antibiotics, interval, and dose compared with ATC standard systems from

WHO. Measurements recommended by WHO is using DDD/100 patient-days. Analysis of the results of phase 1, 2, 3 was performed with Chi square test. If there was one cell that had a value of < 5, then the Fisher 's Exact Test was carried out.

In this study each rectal swab specimens that meet the criteria for inclusion will be used to examine the relationship of intestinal microflora resistance to the quality and quantity of antibiotic use. Subjects performed a rectal swab specimen 1 time when research subjects were out of the hospital. Specimen collection was done by using a cotton-tipped applicator inserted through the anus as deep as 2 cm and then pulled out. The patient was prepared in a prostrate position.

Rectal swab specimens were grown on McConkey medium or EMB. Estimated colonies, for example, the *Escherichia coli*, based on its characteristics, would show red colonies (lactose fermenting), smooth and mucoid colonies when grown on McConkey medium, while EMB medium will appear as metallic sheen colored colonies. The identification of isolated colonies was done using IMViC biochemical test (Indol test, Metyl red, Voges-Proskauer, citrate), by which *Escherichia coli* was shown with IMViC test (+, +,-,-).

Colonies identified as intestinal microflora were grown in Muller Hinton medium disc, then put antibiotic ampicillin, amikacin, cefotaxime, tetra-cycline, ciprofloxacin, and meropenem, and then incubated for 24 hours, then the growth inhibition zone was measured. Measurement of antibiotics use, including antibiotics use, dosage and interval, was based on standard parameters stated by DDD/100 patient-days. Data obtained were analyzed using SPSS 17 and with chi-square and Fisher 's Exact Tests.

RESULTS

In 47 patients treated at surgical wards, 38 received antibiotic therapy, while the other 9 patients did not receive antibiotic therapy. By age group, patients in surgical wards mostly were 20-44 years, consisting 24 (51.06%). The youngest was 24 years and the oldest was 77 years old. Patients in psychiatric wards mostly belonged to age group of 20-44, comprising 42 (89.36%) patients, with the youngest 21 years and the oldest 52 years old. Based on the length of stay (LOS), in surgical wards, the longest day was 107 days and the shortes was 7 days, an average of 25 days with a total length of stay as many as 1160 days. In psychiatric wards, the shortest was 12 days and the longest was 63 days, with an average of 32 days with a total length of stay as many as 1497 days.

Table 1. Distribution of antibiotics in surgical inpatient unit (n = 40) at the Hospital Dr. Soetomo

Types of antibiotics	Surgery		
	Total patients	Total DDD	DDD/ 100px
CTX	1	3.5	0.301724
P	1	5	0.431034
KZ	2	5	0.431034
AZM	1	13.33	1.149138
FOS	5	10.5	0.905172
AMC	3	20.4	1.758621
AML			
MEM	3	28.5	2.456897
MTZ	16	170.33	14.68362
AK	2	36.75	3.168103
CFM	9	35	3.017241
SCF	9	36.25	3.125
CRO	29	362	31.2069
SAM			
LEV			
CAZ			
CN			
TZP			
CIP			

Distribution of antibiotics in surgical inpatient unit

Most antibiotic use in surgical wards was CRO with DDD 362 and DDD/100 patients a day was 31.2069. Lowest antibiotic use was CTX with DDD 3.5 and DDD/100 patient day was 0.301724. In 47 patients with a total length of stay of 1497, amoxicillin and cefixime are antibiotics they used with DDD not much different, which was about 5 to 6.

In the surgical inpatient ward patients with (n = 40), ceftriaxone and cefotaxime showed resistance in the range of 70% and 75%. Tetracycline and ampicillin resistance also showed 82.5% and 97.5%, while amikacin and meropenem showed a sensitivity of 67.5% and 100%. In patients whose rectal rub showed *Escherichia coli* and use of antibiotics (n = 33) obtained ceftriaxone and cefotaxime resistance was 75.8% and 81.8%. Tetracycline and ampicillin resistance was 81.8% and 100%, whereas amikacin and meropenem sensitivity was 69.7% and 100%. In patients who did not use antibiotics (n = 7) the sensitivity of ceftriaxone, cefotaxime, amikacin and meropenem was in the range of 57.1% to 100%,

Table 2. Distribution of resistance significance to antibiotics tested in surgical wards compared to psychiatric wards

Types of antibiotics	Surgery : Psychiatry Significance
[1]CTX	.000
CRO	.000
MEM	
AK	.008
AMP	.000
TE	.000
CIP	.000

CRO = ceftriaxone, MEM = meropenem, AK = amikacin, AMP = ampisislin, TE = tetracycline, CIP = ciprofloxacin

In 47 patients, all antibiotics tested, namely ceftriaxone, cefotaxime, meropenem amikacin, tetracycline, ampicillin and ciprofloxacin, showed a high sensitivity in the range of 64.4% to 100%. In two patients who use antibiotics are 100% resistance to ampicillin and tetracycline, whereas other antibiotics, namely ceftriaxone, cefotaxime, meropenem, amikacin and ciprofloxacin, showed 100% sensitive. In 45 patients, all antibiotics tested, namely ceftriaxone, cefotaxime, meropenem amikacin, tetracycline, ampicillin and ciprofloxacin, high sensitivity was found in the range of 64.4% to 100%.

Resistance results obtained from 40 patients from the surgical wards was be compared to 47 patients from psychiatric wards to find significance level of resistance. Comparison of the results revealed high significant resistance to the drugs tested, i.e cefotaxime, ceftriaxone, amikacin, ampicillin, tetracycline and ciprofloxacin, with $p = 0.000$ to 0.008, $p < 0.05$

DISCUSSION

Frequency of antibiotic use in patients with a long hospitalization is increasing. This was seen in patients treated at surgical wards, where the use of antibiotics was 80.85% (38 of 47 patients using antibiotics) with an average length of stay of 25 days. Most antibiotic use in surgical wards was ceftriaxone with DDD 362 and DDD/100 patient day was 31.2069 days, which means that for every 100 patients there were as many as 31 patients using ceftriaxone of 2 grams per day. The next was metronidazole with DDD 170.33 and DDD/100 patient day was 14.68362, whereas amikacin with DDD 36.75 and DDD/100 patient day was 3.168103. Cefotaxime antibiotic use was lowest with 3.5 and DDD/100 DDD patients today is 0.301724. In surgical wards, antibiotic usage was very high because most of the patients had moderate to severe ilnness and longer length of stay. This is consistent with previous studies that the majority of patients treated using antibiotics due to the severity of the disease as well as consideration of the patient's immune status (Archibald et al 1997). The use of antibiotics in a psychiatric wards was very low, it was amoxicillin with DDD and DDD/100 6 patients a day are 0.400802 and cefixime with DDD 5 and DDD/100 patient 0.334001. This because psychiatric wards had very few patients suffering from bacterial infections.

Of 40 patients in the surgical wards, 7 did not use antibiotics and 33 used antibiotics with *Escherichia coli* in their rectal swab showing resistance to the drug being tested, namely ceftriaxone, cefotaxime, ampicillin, tetracycline, and ciprofloxacin. The percentage range was 70%-97.5%, while meropenem and amikacin was still quite sensitive, by 67% and 100%. This suggests that the induction of antibiotics use can lead to resistance, confirming the research conducted by Thomas Gottlieb and Nimmo in NSW, Australia (Gottlieb & Nimmo 2011).

Patterns of phenotypic resistance in *Escherichia coli* showed ESBL *Escherichia coli* as observed from its resistance to cefotaxime and ceftriaxone antibiotics which are third-generation cephalosporins, but still very sensitive to meropenem (carbapenem class) and amikacin (aminoglycoside class). *Escherichia coli* ESBL is *Escherichia coli* that has an enzyme that can inhibit all classes of beta-lactam antibiotics plus aztreonam.

Seven patients with *Escherichia coli* in rectal swab but without antibiotics showing sensitiveness to the drugs being tested, the cefotaxime, ceftriaxone, meropenem, and amikacin, had a range of percentage of 57.1%-100%. In patients n=40, n=33 and n=7 showed resistance to the drugs being tested, the ampicillin and tetracycline. This is because the microbes *Escherichia coli* has intrinsic or natural resistance to ampicillin and tetracycline, while ciprofloxacin also showed resistance because the resistance can be spread out by porin mutations and pump out (efflux pump).

Of 47 patients examined, 45 patients were not using antibiotics and 2 patients used antibiotics and had rectal swab *Escherichia coli*, 100% sensitive to the drug being tested, ie cefotaxime, ceftriaxone, meropenem, amikacin and ciprofloxacin, while to ampicillin and tetracycline showed 100% resistance. This is because *Escherichia coli* intrinsically or naturally does have a gene resistant to these two drugs tested. This suggests that patients without antibiotics still have full sensitivity to the drugs tested.

Forty-five patients without antibiotic showed high sensitivity to the overall drugs tested, ie cefotaxime, ceftriaxone, meropenem, ampicillin, tetracycline, and ciprofloxacin. This is consistent with the research of Thomas Gottlieb et al. from NSW Australia (Gottlieb & Nimmo 2011). Comparison between wards with high antibiotic use (surgical wards) and wards with lower antibiotics use (psychiatry wards) revealed significant comparison of resistance to the drug being tested, the cefotaxime, ceftriaxone, amikacin, ampicillin, tetracycline and ciprofloxacin with p=0.000 to 0.008, $p < 0.05$. Significance test between surgical wards and psychiatric wards on the drug meropenem, had no value because in both wards overall samples were 100% sensitive, indicating no resistance results.

CONCLUSION

High quantity use of antibiotics can lead to resistance in *Escherichia coli* intestinal microflora. Significance level of antibiotic use in surgical wards in the resistance of *Escherichia coli* intestinal microflora was high $p < 0.000$ on the antibiotics cefotaxime, ceftriaxone, amikacin, ampicillin, tetracycline and ciprofloxacin, as compared to low quantity of antibiotic use in psychiatric wards to the same antibiotics. *Escherichia coli* resistance patterns in the surgical wards showed a phenotypically ESBL *Escherichia coli* that has characteristics of resistance to cefotaxime and ceftriaxone, the third-generation cephalosporin class of antibiotics. However, these antibiotics were still very sensitive to meropenem (carbapenem class) and amikacin (aminoglycoside class).

REFERENCES

Agtini MD, Soeharno R, Lesmana M, Punjabi NH, Simanjuntak C, Wangsasaputra F, Nurdin D, Pulungsih SP, Rofiq A, Santoso H, Pujarwoto H, Sjahrurachman A, Sudarmono P, von Seidlein L, et al (2005). The burden of diarrhoea, shigellosis, and cholera in North Jakarta, Indonesia: findings from 24 months surveillance. BMC Infectious Diseases 5, 89

Alberti C, Brun-Buisson C, Burchardi H, Martin C, Goodman S, Artigas A, Sicignano A, Palazzo M, et al (2002). Epidemiology of sepsis and infection in ICU patients from an international multicentre cohort study. Intensive Care Med 28, 108-121

Ansari F (2001). Use of systemic anti-infective agents in Iran during 1997-1998. Eur J Clin Pharmacol 57, 547-551

Archibald L, Phillips L, Monnet D, McGowan JE Jr, Tenover F, 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

Beekmann SE, Heilmann KP, Richter SS, García-de-Lomas J, Doerna GV (2005). Antimicrobial resistance in *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis* and group A β-haemolytic streptococci in 2002–2003: Results of the multinational GRASP Surveillance Program. International Journal of Antimicrobial Agents 25, 148-156

Bell JM, Turnidge JD, Jones RN (2003). Prevalence of extended-spectrum beta-lactamase-producing *Enterobacter cloacae* in the Asia-Pacific region: results from the SENTRY Antimicrobial Surveillance Program, 1998 to 2001. Antimicrob Agents Chemother 47, 3989-3993

Bronzwaer SL, Cars O, Buchholz U, Mölstad S, et al (2002). A European study on the relationship between antimicrobial use and antimicrobial resistance. Emerg Infect Dis 8, 278-282

Bruinsma N, Stobberingh E, de Smet P, van den Bogaard A (2003). Antibiotic use and the prevalence of antibiotic resistance in bacteria from healthy volunteers in the Dutch community. Infection 31, 9-14

Brunton LL, Lazo JS, Parker KL (2005). Goodman & Gilman's The Pharmacological Basis of Therapeutics, 11th ed., New York, McGraw-Hill, p 675

Duerink DO, Lestari ES, Hadi U, Nagelkerke NJD, et al (2007). Determinants of carriage of resistant *Escherichia coli* in the Indonesian population inside and outside hospitals. J Antimicrob Chemother 60, 377-384

Erb A, Stürmer T, Marre R, Brenner H (2007). Prevalence of antibiotic resistance in *Escherichia coli*: overview of geographical, temporal, and methodological variations. Eur J Clin Microbiol Infect Dis 26, 83-90

Farra A, Skoog G, Wallén L, Kahlmeter G, Kronvall G, Sörberg M (2002). Antibiotic use and *Escherichia coli* resistance trends for quinolones and cotrimoxazole in Sweden. Scand J Infect Dis 34, 449-455

Filius PM, Gyssens IC, Kershof IM, Roovers PJ, et al (2005). Colonization and resistance dynamics of gram-negative bacteria in patients during and after hospitalization. Antimicrob Agents Chemother 49, 2879-2886

Gottlieb T and Nimmo GR (2011). Antibiotic resistance is an emerging threat to public health: an urgent call to action at the Antimicrobial Resistance Summit 2011. Med J Aust 194, 281-283

Hsueh PR, Liu CY, Luh KT (2002). Current status of antimicrobial resistance in Taiwan. Emerging Infectious Diseases 8, 132-137

Hu S, Liu X, Peng Y (2003). Assessment of antibiotic prescription in hospitalised patients at a Chinese university hospital. J Infect 46, 161-163

Ieven M, van Looveren M, Sudigdoadi S, Rosana Y, et al (2003). Antimicrobial susceptibilities of *Neisseria gonorrhoeae* strains isolated in Java, Indonesia. Sex Transm Dis 30, 25-29

Kuntaman, Lestari ES, Severin JA, Kershof IM, Mertaniasih NM, Purwanta M, Hadi U, Johnson JR, et al (2005). Fluoroquinolone-resistant *Escherichia coli*, Indonesia. Emerging Infectious Diseases 11, 1363-1369

Lesmana M, Subekti D, Simanjuntak CH, Tjaniadi P, Campbell JR, Oyofo BA (2001). Vibrio parahaemolyticus associated with cholera-like diarrhea among patients in North Jakarta, Indonesia. Diagn Microbiol Infect Dis 39, 71-75

Lesmana M, Subekti DS, Tjaniadi P, Simanjuntak CH, Punjabi NH, Campbell JR, Oyofo BA (2002). Spectrum of vibrio species associated with acute diarrhea in North Jakarta, Indonesia. Diagn Microbiol Infect Dis 43, 91-97

McDonald LC, Chen FJ, Lo HJ, Yin HC, Lu PL, Huang CH, Chen P, Lauderdale TL, Ho M (2001). Emergence of reduced susceptibility and resistance to fluoroquinolones in *Escherichia coli* in Taiwan and contributions of distinct selective pressures. Antimicrob Agents Chemother 45, 3084-3091

NNIS System (2003). National Nosocomial Infections Surveillance (NNIS) System Report, data summary from January 1992 through June 2003, issued August 2003. Am J Infect Control 31, 481-498

Okeke IN, Klugman KP, Bhutta ZA, Duse AG, Jenkins P, et al (2005). Antimicrobial resistance in developing countries. Part II: strategies for containment. Lancet Infect Dis 5, 568-580

Shears P (2001). Antibiotic resistance in the tropics. Epidemiology and surveillance of antimicrobial resistance in the tropics. Trans R Soc Trop Med Hyg 95, 127-130

Sheng WH, Chen YC, Wang JT, Chang SC, Luh KT, Hsieh WC (2002). Emerging fluoroquinolone-resistance for common clinically important gram-negative bacteria in Taiwan. Diagn Microbiol Infect Dis 43, 141-147

Subekti DS, Lesmana M, Tjaniadi P, Machpud N, Sriwati, Sukarma, Daniel JC, Alexander WK, et al (2003). Prevalence of enterotoxigenic *Escherichia coli* (ETEC) in hospitalized acute diarrhea patients in Denpasar, Bali, Indonesia. Diagn Microbiol Infect Dis 47, 399-405

Tjaniadi P, Lesmana M, Subekti D, Machpud N, Komalarini S, Santoso W, Simanjuntak CH, et al (2003). Antimicrobial resistance of bacterial pathogens associated with diarrheal patients in Indonesia. Am J Trop Med Hyg 68, 666-670