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ARTICLE

Antimicrobial resistance among commensal isolates of *Escherichia coli* and *Staphylococcus aureus* in the Indonesian population inside and outside hospitals

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Abstract The prevalence of antimicrobial resistance among the commensal microflora was examined in the Indonesian population inside and outside hospitals. A total of 3,995 individuals were screened in two major urban centers. Among *Escherichia coli* from rectal samples (n= 3,284) the prevalence of resistance to ciprofloxacin and other classes of antibiotics was remarkably high, especially in individuals at the time of discharge from hospital. *Staphylococcus aureus* isolates (n=361) were often resistant to tetracycline (24.9%), but this was not associated with hospital stay. Two *S. aureus* isolates harbored the *mecA* gene. Regional differences in resistance rates exist, suggesting regional differences in selection pressure, i.e., antibiotic usage patterns. The results show that antimicrobial resistance among commensal *E. coli* and *S. aureus* has emerged in Indonesia.

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Introduction

Antimicrobial resistance has become a major health problem worldwide, both in hospitals and the community [1–5]. The emergence of antimicrobial resistance is correlated with selective pressure from the use, often inappropriate, of antimicrobial agents [1–5] and results in increased mortality, morbidity, and health care costs [2]. Data on the epidemiology of antimicrobial resistance is important and can be drawn from three general sources: surveillance,

outbreak investigations, and prospective studies [2]. Resistance data may be gathered either from clinical isolates or from isolates cultured from the commensal microflora of individuals in the absence of infection [6–9]. Surveillance of antimicrobial resistance has been reported in many countries, including developing countries in the Far East [10–23]. However, resistance data from Indonesia are limited to bacterial pathogens isolated from patients with infections, especially diarrheal disease [15–19]. No data exist on the presence of resistance among potential pathogens in the commensal flora of Indonesian people. Such data are relevant, as they should provide a basis for the selection of empiric use of antimicrobial agents, either for therapy or for prophylaxis. Therefore, the aim of this study was to investigate antimicrobial resistance rates among potential pathogens in the commensal microflora of representative cohorts of people in two major urban centers in Indonesia.

Materials and methods

Population

Two university hospitals, Dr. Soetomo Hospital in Surabaya, East Java, and Dr. Kariadi Hospital in Semarang, Central Java, Indonesia, and three primary health centers (two in Surabaya and one in Semarang) were selected for this study. Four thousand individuals were targeted to be screened constituting four different populations in each of the two cities (500 individuals per population group per city). Group 1 consisted of patients being admitted to the hospital (admission group), group 2 were patients being discharged from the hospital (discharge group), group 3 contained ambulatory patients visiting primary health centers (puskesmas group), and group 4 consisted of relatives of patients being admitted to the hospital in each of the two cities (relatives group). Patients at admission and discharge were selected from four hospital departments: internal medicine, surgery, obstetrics and gynecology, and pediatrics. Individuals were excluded from the study if they were transferred from another hospital, if they were not accompanied by a family member (admission group), or if they had been admitted to a hospital within the previous 3 months (admission group, puskesmas group and relatives group). Approval of the medical ethics committees was obtained before the start of the study. Only patients who had given their informed consent were included.

Bacterial isolation

Rectal and nasal samples were taken with sterile, cotton-tipped swabs, and these were put in Amies transport medium (Copan, Brescia, Italy) and transported in closed boxes at ambient temperature to the laboratory on the same day. All swabs were cultured within 24 h. Rectal swabs were cultured on CHROMagar Orientation (Becton Dickinson, Heidelberg, Germany) for isolation of *Escherichia coli* [24]. From each swab, two colonies representing the dominant growth in the fecal flora were collected. Pink colonies were assumed to be *E. coli* and were used for susceptibility testing without additional identification testing. Nasal swabs were cultured by using phenol red mannitol agar (Becton Dickinson, Heidelberg, Germany) for isolation of *Staphylococcus aureus.* In the Netherlands, all probable *S. aureus* isolates were identified by a latex agglutination test (Staphaurex Plus, Abbott, Murex, Chatillon, France) and the Vitek 2 system (bioMérieux, Marcy l'Etoile, France). In case of doubt, an *S. aureus*-specific DNA hybridization test (Accuprobe, Genprobe inc., San Diego, CA, USA) was performed.

Antimicrobial susceptibility testing

Antimicrobial susceptibility testing of the isolates was performed in Indonesia by disk diffusion as recommended by the Clinical and Laboratory Standards Institute (CLSI; formerly the NCCLS) [25]. Disks loaded with the following antimicrobial agents (Oxoid, Basingstoke, UK) were used for susceptibility testing of *E. coli*: gentamicin, chloramphenicol, trimethoprim/sulfamethoxazole, ampicillin, cefotaxime, and ciprofloxacin. One *E. coli* isolate per patient was included in the analysis. Tetracycline, oxacillin, gentamicin, erythromycin, chloramphenicol, and trimethoprim/sulfamethoxazole disks were used for susceptibility testing of *S. aureus*. The performance of the susceptibility testing was monitored twice weekly by the quality control strains *E. coli* ATCC 25922 and *S. aureus* ATCC 25923.

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PCR for *mecA* gene detection

Polymerase chain reaction (PCR) for *mecA* gene detection was performed with primers MEC1 (5′- AAA ATC GAT GGT AAA GGT TGG C- 3′) and MEC2 (5′- AGT TCT GCA GTA CCG GAT TTG C- 3′), which generate a 533-bp product as described previously [26]. Bacterial DNA was isolated on a MagNA Pure LC™ with MagNA Pure LC DNA Isolation Kit III for bacteria and fungi (Roche Molecular Biochemicals, Mannheim, Germany). DNA concentration was assessed spectrophotometrically. PCR program was performed under the following conditions: predenaturation for 4 min at 94°C; 25 cycles of 45 s at 94°C, 45 s at 55°C, and 45 s at 72°C, and a final extension step of 5 min at 72°C. PCR products were resolved in a 1% agarose gel in 0.5 Tris-borate + ethylene-diaminetetraacetate (TBE) stained with ethidium bromide and visualized under ultraviolet (UV) light. A positive and a negative control were included in each PCR run.

Statistical analysis

Statistical comparisons of antibiotic resistance between the strains collected from the four different groups and between similar groups in the two cities were made by using the chi-square analyses or Fisher's exact test (two-tailed). Data were analyzed by using the statistical software package SPSS version 11.5 for Windows (SPSS Inc. Chicago, IL, USA). A p value < 0.05 was considered significant.

Results

A total of 3,995 individuals were screened between July and October 2001 in Surabaya and between January and May 2002 in Semarang. We collected 5,535 *E. coli* strains from 3,284 individuals and 362 *S. aureus* isolates from as many individuals.

Resistance among *E. coli*

E. coli isolates (3,284) showed considerable levels of resistance against a number of commonly used antibiotics (Table 1). For most antimicrobials, the lowest resistance rates were measured in *E. coli* isolated from the relatives group, whereas the highest rates were measured in patients in the discharge group. For all antimicrobials, resistance rates on discharge were higher compared with those in patients on admission, relatives, and patients visiting a primary health center. Substantial resistance rates toward chloramphenicol, trimethoprim/sulfamethoxazole, and ampicillin were observed among *E. coli* cultured from patients visiting primary health centers compared with *E. coli* from the relatives group. Resistance toward gentamicin, cefotaxime, and ciprofloxacin was low on admission to the hospital. However, high rates of resistance against these latter antibiotics were found among *E. coli* cultured from patients at the time of discharge from the hospital.

Table 1 Antimicrobial resistance rates [*n* (%)] of *Escherichia coli* and *Staphylococcus aureus* from different cohorts in Indonesia

	Admission	Discharge	Relatives	Primary health center (puskesmas)	Total
E. coli	*n*=822	*n*=784	*n*=815	*n*=863	*n*=3,284
Gentamicin	32 (3.9)[a]	141 (18.0)[d,e]	11 (1.3)[c]	18 (2.1)[b]	202 (6.2)
Chloramphenicol	210 (25.5)[a]	335 (42.7)[d,e]	64 (7.9)[c]	95 (11.0)[b,f]	704 (21.4)
Trimethoprim/sulfamethoxazole	342 (41.7)[a]	435 (55.5)[d,e]	164 (20.1)[c]	209 (24.2)[b,f]	1,150 (35.0)
Ampicillin	416 (50.6)[a]	571 (72.8)[d,e]	162 (19.9)[c]	271 (31.4)[b,f]	1,420 (43.2)
Cefotaxime	17 (2.1)[a]	98 (12.5)[d,e]	6 (0.7)[c]	8 (0.9)	129 (3.9)
Ciprofloxacin	48 (5.8)[a]	173 (22.1)[d,e]	17 (2.1)[c]	17 (2.0)[b]	255 (7.8)
S. aureus	*n*=84	*n*=98	*n*=82	*n*=97	*n*=361
Tetracycline	29 (34.5)	24 (24.5)	18 (22.0)	19 (19.6)[b]	90 (24.9)
Oxacillin	0 (0)	2 (0.6)	0 (0)	0 (0)	2 (0.6)
Gentamicin	2 (2.4)	1 (1.0)	0 (0)	1 (1.0)	4 (1.1)
Erythromycin	4 (4.8)	5 (5.1)	1 (1.2)	2 (2.1)	12 (3.3)
Chloramphenicol	12 (14.3)	9 (9.2)	7 (8.5)	6 (6.2)	34 (9.4)
Trimethoprim/sulfamethoxazole	10 (11.9)	7 (7.1)[d]	7 (8.5)	0 [b, f]	24 (6.6)

Resistance rates were compared in defined pairs (see a–f), using the chi-square test or Fisher's exact test, as applicable (p<0.05 was considered significant)

[a] Significant difference for admission vs. discharge
[b] Significant difference for admission vs. puskesmas
[c] Significant difference for admission vs. relatives
[d] Significant difference for discharge vs. puskesmas
[e] Significant difference for discharge vs. relatives
[f] Significant difference for puskesmas vs. relatives

Resistance among *S. aureus*

The rate of nasal carriage of *S. aureus* was 362 out of 3,995 (9.1%) individuals. One strain of *S. aureus* did not grow on the Mueller Hinton agar plate for antimicrobial susceptibility testing. Overall, 90/361 (24.9%) *S. aureus* strains were resistant to tetracycline and 2/361 (0.6%) were resistant to oxacillin (Table 1). The two oxacillin-resistant strains of *S. aureus* harbored the *mecA* gene. Resistance rates against tetracycline among patients on admission were higher compared with rates found in patients visiting the primary health centers ($p=0.022$). For trimethoprim/sulfamethoxazole, the resistance rates among isolates from patients on admission, patients on discharge, and from relatives of patients on admission were higher compared with the rates among *S. aureus* isolates from patients visiting primary health centers ($p<0.001$, $p=0.013$, and $p=0.007$, respectively).

Geographical differences

When comparing resistance data of *E. coli* and *S. aureus* isolated in Semarang with those isolated in Surabaya, the overall trends observed were similar. However, some striking differences became obvious. For *E. coli*, the resistance rates among patients at discharge in Semarang were higher than those observed in Surabaya for all antibiotics except for gentamicin (data not shown). Also, more resistance among *E. coli* was observed in Semarang compared with Surabaya with regard to ampicillin [792/1,707 (46.4%) in Semarang vs. 628/1,577 (39.8%) in Surabaya; $p<0.001$)] In contrast, chloramphenicol resistance was higher among *E. coli* isolated from Surabaya patients on admission [117/389 (30.1%) in Surabaya vs. 93/433 (21.5%) in Semarang; $p=0.005$] and likewise when comparing isolates from their relatives [38/383 (9.9%) in Surabaya vs. 26/432 (6.0%) in Semarang; $p=0.05$].

With regard to *S. aureus*, the rates of resistance to trimethoprim/sulfamethoxazole in the admission and relatives groups and tetracycline resistance in the discharge group in Surabaya were much higher than in Semarang (data not shown).

Discussion

This study is the first population-based study of antimicrobial resistance among common pathogenic bacteria in the commensal microflora of several groups of individuals in Indonesia. We stress the fact that the strains examined in the present study were not isolated from clinical materials as in previous studies but from the normal flora of the anterior nares and from the rectum of individuals with a variety of diseases as well as from healthy persons. We targeted our surveillance of antimicrobial resistance towards *E. coli* and *S. aureus,* as they can be considered sentinel species of microorganisms for the emergence of resistance [6–9]. Analyses of possible risk factors for the carriage of resistant microorganisms, such as demographic, socioeconomic, disease-related and healthcare-related determinants as well as recent antibiotic use will be described elsewhere.

We showed that antibiotic resistance rates among *E. coli* isolated from patients on discharge from the hospital are consistently higher than previously described. An earlier study in Indonesia by US Naval Medical Research Unit #2 (NAMRU-2) [16] showed that resistance rates for ampicillin, chloramphenicol, and trimethoprim/sulfamethoxazole among clinical isolates of enterotoxigenic *E. coli* (ETEC) were higher than in our study. In contrast, our study yielded higher rates of ciprofloxacin resistance compared with that study. There are no earlier data about resistance rates of *E. coli* against gentamicin and cefotaxime in Indonesia. However, in a survey performed in Indonesian hospitals in the late 1990s, 23.3% of *E. coli* had an extended-spectrum beta-lactamase phenotype [14].

From a series of studies that were conducted through the 1980s and 1990s in Taiwan, 100% of clinical isolates of *E. coli* proved susceptible to fluoroquinolones (norfloxacin, ofloxacin, and ciprofloxacin) until 1996. By 1996–1997, 20% of *E. coli* had become resistant to ciprofloxacin, and 48% of patients with ciprofloxacin-resistant *E. coli* reportedly had not used any fluoroquinolones [27]. Another study from Taiwan reported that the ciprofloxacin resistance rate among *E. coli* was 11.3% between August and December 1998, [28] 0% in 1998–1999 by the SENTRY surveillance program, [23] and 46% in 1999 by the National Taiwan University Hospital study (NTUH) [29]. Data of antimicrobial resistance of clinical isolates of *E. coli* against ciprofloxacin from other countries have also been reported by the SENTRY global antimicrobial surveillance program: 61% in Hong Kong, 93% in mainland China, 75% in Singapore, and 54% in the Philippines [23]. In Korea, the Korean Nationwide Surveillance of Antimicrobial Resistance Study (KONSAR) reported a rate of 28%, [30], and the Taiwan Surveillance of Antimicrobial Resistance (TSAR) reported 12% in Taiwan [31]. Although in all studies clinical isolates of *E. coli* were used, it is clear that fluoroquinolone resistance is now prevalent in most countries in Asia, including Indonesia. The genetic backgrounds and virulence characteristics of the Indonesian fluoroquinolone-resistant *E. coli* from the present study have recently been described by Kuntaman et al. [32].

Multiple studies have reported high frequencies of methicillin-resistant *S. aureus* (MRSA) among clinical isolates of *S. aureus* in Asia. The rate of MRSA among

clinical *S. aureus* isolates was more than 50% in Korea in 1997 [11, 33] and more than 60% in Taiwan between 1993 and 1999 [10, 34]. In Japan it was 35.8% in 1987 and has increased to 67.3% in 1989 [35]. Another study in Japan showed that the frequency of MRSA was 22–64% in 1988, 22–69% in 1989, and 29–76% in 1990, and increasing yearly [21]. Furthermore, *S. aureus* with reduced susceptibility to vancomycin has been found in hospitals in several Asian countries [36].

In this study, we found that methicillin resistance in *S. aureus* was 2/361(0.6%) isolates from Indonesia. These oxacillin-resistant strains of *S. aureus* harbored the *mecA* gene. This finding suggests that MRSA has not yet gained a strong foothold in the Indonesian archipelago. Only two of 3,995 (0.05%) persons screened harbored MRSA, which compares favorably with the 0.84% MRSA carrier rate found in the same period in a population-based screening study in the USA [37]. However, as we did not include clinical strains causing nosocomial infections in this study, we cannot exclude the possibility that MRSA has emerged in some hospital settings in Indonesia. Of note, the overall rate of *S. aureus* nasal carriage in our study was only 9.1%, i.e., much lower than the 20% or higher levels generally found among populations in Western countries [38]. Low carriage rates of *S. aureus* among the Indonesian population may, by itself, reduce or interfere with the spread and emergence of MRSA variants.

There are no prior data about the prevalence of antibiotic resistance of commensal *S. aureus* against tetracycline, gentamicin, erythromycin, chloramphenicol, and trimethoprim/sulfamethoxazole in Indonesia. When we compare our findings with recent data from Taiwan [39], the prevalence of antimicrobial resistance among clinical isolates of *S. aureus* was higher in Taiwan than in Indonesia. The resistance rates for tetracycline were 71% and 24.9%, for oxacillin 60% and 0.6%, for gentamicin 51% and 1.1%, for erythromycin 73% and 3.3%, for chloramphenicol 29% and 9.4%, and for trimethoprim/sulfamethoxazole 42% and 6.6% in *S. aureus* from Taiwan and from Indonesia (this study), respectively. Antimicrobial resistance profiles of clinical isolates of *S. aureus* have also been reported from Korea [22], showing that the resistance rates of methicillin-sensitive *S. aureus* (MSSA) and MRSA against tetracycline were 22% and 90%, against gentamicin 28% and 95%, against erythromycin 37% and 98%, and against trimethoprim/sulfamethoxazole 1% and 9% in MSSA and MRSA, respectively. In contrast to our study, the Taiwanese and Korean surveillance systems were based on clinical samples and not on sampling of commensal flora, as was done in this study. Thus, direct comparison is not valid, as resistance rates among clinical isolates of *S. aureus* may well be higher in Indonesia also.

In conclusion, we show that antimicrobial resistance among *E. coli* and *S. aureus* present in the commensal microflora of people has emerged in Indonesia. Among *E. coli*, the prevalence of resistance to ciprofloxacin and other antibiotics is remarkably high, especially in individuals after hospitalization. Although the prevalence of MRSA is low, tetracycline resistance is common among *S. aureus* and not associated with hospital stay. Within Indonesia, regional differences in resistance rates exist, suggesting regional differences in selection pressure, i.e., antibiotic usage patterns. Moreover, for *S. aureus*, resistance rates of isolates from patients at discharge from the hospital were no higher than on admission, whereas these rates in *E. coli* were significantly higher on discharge. Therefore, resistance in *E. coli* appeared to be both community and hospital associated, whereas resistance in *S. aureus* seems to be mainly community derived. This is an important finding for future strategies that target the containment of antimicrobial resistance in Indonesia.

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