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Study of Antibiogram and Drug Resistance for some Bacterial Infection from the Human Internal Fluid (CSF, Ascitic Fluid and Synovial Fluid)

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Abstract: Antibiograms are often taken into account to define a rational selection of an empirical antimicrobial therapy for human internal fluids of treating patients with hospital-acquired infections. This study has performed a paired comparison between the antibiogram constructed with laboratory-based data and that formed with data subjected to prior clinical validation. Hence, the study was designed to determine the antibiogram of the various species of resistant pathogenic bacterium associated with hospital-acquired infection on human internal ascitic fluids. Cumulative resistance rates were estimated in parallel at the laboratory with the whole data and at the infection control department with data subjected to prior clinical validation. Results shows that no significant differences survived ($p>0.05$) between the percentage of isolates resistant from the infection-based system and laboratory-based system for all antimicrobial-resistant organisms studied, except methicillin resistance in *Staphylococcus* species. The mean difference in percentage resistance was higher from the infection-based system than the laboratory-based system for *S. aureus* (mean difference + 8%, $p<0.001$) and coagulase-negative *Staphylococci* (mean difference, + 9%, $p<0.001$). Overall, hospital antibiograms reflected susceptibility patterns among isolates associated with hospital-acquired infections. Thus, in conclusion, the Laboratory-based data underestimates the frequency of several major resistant organism in-patients with hospital-acquired infection. Previous clinical validation of the individual susceptibility reports seems to be a suitable strategy to get more reliable data.

Key words: Pathogenic organisms, antimicrobial agents, surveillance and antibiogram analysis

INTRODUCTION

The whole world filled with a bewildering array of infection agents. Infection is a part and parcel of the life of human, animals and plants (Zapantis *et al*., 2005a). Face is the mirror index of mind is the proverb, like wise human body fluid is the source of identification of infection (Zazava *et al*., 1995). Susceptibility statistics, consisting of the cumulative and ongoing summary of the patterns of antimicrobial susceptibility of clinically important bacteria, are important to various health care practitioners, including physicians, pharmacists, infection control personnel and microbiologists (Magee, 2004; Tenover, 2006). Currently there are no standards by which isolates should be included in these summary data, although such guidelines are in development by the National Committee for Clinical Laboratory Standards (NCCLS). Many issues regarding generating these reports, such as handling duplicate isolates, incorporation of only select sites of cultures or isolates from only confirmed infections are currently being discussed by NCCLS. The frequency of antimicrobial resistance among isolates from patients with infections acquired in the health care setting may be different from that among all isolates processed by the clinical microbiology laboratory (Bantar *et al*., 2007). Such reports would be difficult to generate by many clinical microbiology laboratories. Validating the clinical relevance of all-isolate summaries for health care-acquired infections would provide support for the current widespread practice of using a single summary report in most hospitals (Anthony *et al*., 2001). Still, there was no one studies carried out this kind of clinical laboratory oriented validation based work. Hence, this study has undertaken the objective to determine the antibiogram of the various species of resistant pathogenic bacterium associated with hospital-acquired infection on human internal ascitic fluids.

MATERIALS AND METHODS

Surveillance data and sites: Hospitals that participate in the ICU surveillance component of the NNIS-ICU system

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were invited to participate in Project ICAE and 35 hospitals representing 146 ICUs submitted data to Project ICARE and the ICU component of the NNIS system during the study period January 2005-April 2006.

Infection-based reports: Participating hospitals reported monthly hospital-acquired infection data from at least one ICU to NNIS-ICU. The NNIS-ICU data include information on all hospital-acquired infections (infections occurring at any site) detected in patients during the month in which active surveillance occurred in the ICU. The susceptibility interpretation (susceptible, intermediate and resistant) for drugs tested against each pathogen associated with the hospital-acquired infection is reported according to NCCLS breakpoint definitions (Rice *et al*., 1996; Dijkshoorn *et al*., 2001). This allows for determining the cumulative susceptibility report or antibiogram, of all pathogens associated with hospital-acquired infections during that month (hospital-acquired infection-based cumulative antibiogram).

Laboratory-based reports: As part of NNIS-ICARE, hospitals also reported susceptibility data to select organisms from clinical specimens (CSF, ascitic fluid and synovial fluid) obtained from patients in these same ICUs, whether associated with hospital-acquired or community-acquired infection or colonization. This allowed for determining the cumulative susceptibility report, or antibiogram, of all organisms processed from clinical specimens submitted to the clinical microbiology laboratory (laboratory-based cumulative antibiogram).

Data analysis: Data was analyzed by SAS version. For each ICU, only months in which data was reported to both NIS-ICU and NIS-ICAE were selected for analysis. For all of the suitable unit-months, collective data (cumulative data combining all eligible unit-months for each ICU) about each organism were compared between the laboratory-based and infection-based reporting systems within each ICU. The testing rates (number of isolates tested against a specified antimicrobial per month) and prevalence rates of resistance (percentage of isolates tested that were resistant) were calculated for each reporting system. Eight prevalent resistant isolates were calculated to the specified antimicrobial in the pooled data and included as following combination. Initially, methicillin-resistant for *Staphylococcus aureus* (MRSA), methicillin-resistant coagulase-negative staphylococci, vancomycin-resistant for *Enterococcus* species. Though, *E. coli* organism revealed as five different kinds of antibiotic substances such as profloxacin-resistant or ofloxacin-resistant for *Escherichia coli*; ceftazidime-resistant, Cefotaxime-resistant or Ceftriaxone (third-generation cephalosporin). Then third-generation resistant shows cephalosporin for *Klebsiella pneumoniae*; third-generation cephalosporin-resistant for *Enterobacter* species followed by piperacillin-resistant for *Pseudomonas aeruginosa*. Finally, ceftazidime-resistant *P. aeruginosa* imipenem resistant *P. aeruginosa* and ciprofloxacin-resistant or ofloxacin-resistant *P. aeruginosa*.

Further analysis included pair wise comparisons of the average number of isolates tested per month and the average difference in resistance rate (infection-based rate minus laboratory-based rate). Pair wise comparisons were performed to measure the difference between reporting systems (laboratory based vs. infection based) within each ICU. A χ^2 test was performed to test the homogeneity of the differences among all ICUs. These comparisons were aggregated to determine statistical significance. If the differences were homogeneous, a weighted mean was calculated and tested against zero by means of a Z-test to determine a p-value. In case of non-homogeneity, the average difference was also tested against zero by means of a Z-test.

To augment surveillance for Antimicrobial resistance at hospitals in the United States, the Hospital Infections Program at Centers for Disease Control and Prevention (CDC), in collaboration with the Rollins School of Public Health of Emory University, began Project ICARE (Intensive Care Antimicrobial Resistance Epidemiology) in 1996 at a subset of hospitals participating in CDC's National Nosocomial Infections Surveillance (NNIS) system. Project ICARE hospitals reported data on all strains of selected bacteria tested in the clinical microbiology laboratory by Yan (2006). These data allowed for determination of prevalence rates of resistance similar to the routine hospital cumulative antibiogram. The cumulative antibiogram or cumulative susceptibility test data report is the percentage of isolates of a given species tested in a given institution or specific areas of the institution, that are susceptible or resistant to each of the antimicrobial agents routinely tested. Here used data gathered from hospitals participating in this study differences in the prevalence of resistance in participating Intensive Care Units (ICUs). Validation of the clinical relevance of the routine hospital antibiogram would increase the confidence level among clinicians that laboratory-based data can guide empiric therapy for patients with hospital-acquired infections.

Antimicrobial susceptibility test: All the isolates that were potential human pathogens were subjected to antimicrobial susceptibility test using the agar diffusion

method on Mueller Hinton agar. The antimicrobial agents used and the disk concentrations were Benzyl penicillin 1.5 units, Ampicillin 25 mcg, Tetracycline 10 mcg/25 mcg for gram positive and gram negative organisms, respectively, Chloramphenicol 25 mcg, Gentamycin 10 mcg, Ciprofloxacin 10 mcg, Cloxacillin 10 mcg Cotrimoxazole 25 mcg, Ceftazidine 10 mcg and Augmenting 30 mcg. Laboratory maintained susceptible strains were used as control.

RESULTS

Frequency of organism testing: For the 19 antimicrobial-resistant organisms evaluated the ICU-specific average number of organisms tested for susceptibility varied by organism, antimicrobial agent tested and reporting system. In the laboratory-based system, the testing rate for *S. aureus* and coagulase-negative staphylococci tested to methicillin group agents was highest (median values of 3.1 and 3.3 organisms tested per month, respectively), whereas *Enterobacter* species tested for third-generation cephalosporin susceptibility was lowest (median value of 1.4 organisms per month). In contrast, the average testing rate by the infection-based system (organisms associated with a hospital-acquired infection) was consistently per month. Therefore, the testing rate of the laboratory-based system was 4-fold higher than for the infection-based reporting (Table 1).

Figure 1 clearly shows that the antibiogram of the three pathogenic bacterial organisms, among the four, dominantly *E. coli* having better response followed by *S. pneumoniae* but *N. meningitis* showed comparatively decreased response in antibiogram.

Prevalence of resistance to antimicrobial agents: The prevalence of resistance to antimicrobial agents from the study hospitals reporting to the infection-based system (Table 2) was similar to that previously reported from the all NIS hospitals reporting data from ICU patients. For the 10 antimicrobial-resistant organisms evaluated, the number of ICUs testing 6 organisms was consistently higher when used data from the laboratory-based reporting system (median value, 100, range, 50-100 ICUs) than the infection-based system (median value, 26, range 10-100 ICUs). Therefore, comparisons between the 2 reporting systems is limited to those ICUs that reported susceptibility results on a sufficient numbers of organisms by the infection-based system.

It included data from ICUs that reported sufficient data (>10 isolates) to both laboratory based and infection based reporting system, National Nosocomial Infection Surveillance System January 2005-April 2006, IBRS, Infection based reporting system, Laboratory Based reporting system and prevalence of resistance.

The prevalence rates of resistance to antimicrobial agents among all ICUs were usually higher among isolates reported to the infection-based system than among

Table 1: Antibiogram of the bacteria identified in the samples investigated

	Body fluids									
	C.S.F fluid					Ascitic fluid				
Name of the antibiotics	*Streptococcus pneumoniae* (+)	*Klebsiella pneumoniae* (-)	*Neisseria meningitidis* (-)	*Escherichia coli* (-)	*Escherichia coli* (-)	*Escherichia coli* (-)	*Klebsiella pneumoniae* (-)	*Klebsiella pneumoniae* (-)	*Citrobacter freundii* (-)	*Streptococcus pneumoniae* (+)
Amikacin	S (35)	-	R	S (40)	-	S (35)	R	S (35)	S (35)	R
Ampicillin + sulbctum	-	-	-	-	-	S (35)	-	-	-	-
Amoxycillin	-	R	-	R	R	R	R	R	-	R
Amoxyclav	R	R	-	R	R	R	R	R	-	R
Cefotaxime	-	-	S (35)	-	S (30)	S (45)	S (50)	-	R	-
Cefepime	S (30)	-	-	-	-	-	-	-	-	S (30)
Cefixime	-	S (45)	-	-	-	S (50)	-	R	-	-
Ceftriaxone	S (40)	-	-	S (40)	S (40)	-	-	R	R	R
Cephalexin	R	R	-	S (35)	S (40)	-	-	S (40)	R	-
Cefdinir	S (30)	S (40)	S (40)	-	-	-	-	R	R	-
Ciprofloxacin	-	-	-	S (35)	-	-	R	-	-	-
Clindamycin	-	-	-	-	-	-	-	-	R	-
Cloxacillin	-	-	-	-	-	-	-	-	-	S (35)
Gatiflex	-	-	-	-	-	-	S (40)	-	S (35)	-
Gentamycin	S (35)	-	R	S (35)	S (35)	S (35)	S (45)	R	S (50)	R
Ofloxacin	-	-	-	S (40)	-	-	-	-	S (50)	-
Pefloxacin	-	-	-	-	-	-	-	-	S (45)	-
Penicillin	R	R	S (40)	-	-	-	-	-	-	S (40)
Sparflox	-	-	-	S (30)	-	-	S (45)	-	S (40)	-

S: Sensitivity to the antibiotic, R: Resistance to the antibiotic, +: Gram positive bacteria, -: Gram negative bacteria

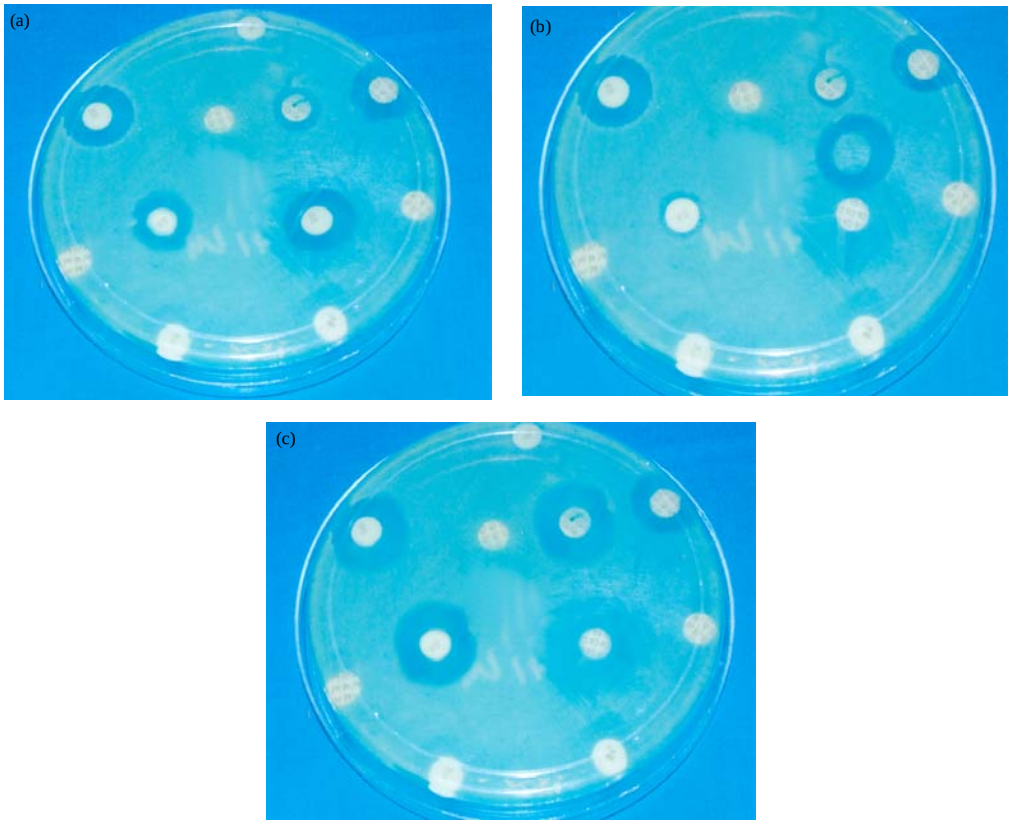

Fig. 1 (a-c): The antibiogram of the three different types of pathogenic bacterial orgamsms (a) *Streptococcus pneumoniae* (b) *Neissaria meningitis* and (c) *Escherichia coli*

Table 2: Testing rates to select organisms of specific antimicrobial agents and the ratio of testing rates among intensive care units (ICUs)

Tested organisms	Antimicrobial agent[a]	Medium testing rate[b]	IBRS LPRS	Ratio of testing rates	25-75th Percentile[c]
Staphylococcus aureus	Oxacilline	1.2	3.4	5.1	2.8-7.3
Enterococcus sp.	Ciprofloxacin	1.4	1.8	5.2	3.2-5.7
Staphylococci (negative)	Ceftazimide[d]	1.0	3.0	5.7	4.5-8.3
Klepsiella pneumonea	Imipenem	0.7	1.7	3.5	3.1-4.5
E. coli	Ceftazimide[d]	0.5	2.5	45	2.6-8.5
E.nterobactor species	Quinolone	0.6	2.8	5.2	3.7-9.1
Pseudomonas aeruginosa	Piperacillin	1.5	1.8	3.1	3.1-8.1
P. aeruginosa	Gentamycin	0.8	2.5	6.3	3.4-5.8
P. aeruginosa	Pefloxacin	0.7	2.9	3.5	2.8-5.5
P. aeruginosa	Ofloxacin	1.5	2.1	4.6	3.0-5.6

[a]ICUs reported testing≥10 isolates to both the Nesocomial Infections Surveillance system ICU component infection based reporting system) or Nosocomial Infection system. Intensive Care Antimicrobial Epidemiology (Laboratory based reporting system (LBRS) (January 2005-April 2006.) IBRS Infection based reporting system, LBRS, Laboratory based reporting system. Quinolone indicates Ofloxacine (or) Ciprofloxacine. [b]Testing rate is the average number of isolates tested against specific antimicrobials per month fro all data in an ICU. [c]Median and 25th percentiles of all testing rates (No. of isolates tested by laboratory based system divided by the number tested by infection based system) for the organism listed. [d]Organisms tested against ceftazidime, cefrriazone or cefotaxamine

isolates reported to the laboratory-based system (Table 2). However, these differences were rarely statistically significant when we used the pair wise comparison which takes into account the differences observed within each ICU and the consistency with which these differences were observed. There were 2 notable exceptions such as by use of the pair wise comparisons, infection-based prevalence of resistance was significantly higher than laboratory-based prevalence for MRSA (average difference+7.1%; $p<0.005$) and methicillin-resistant coagulase-negative *staphylococci* (mean difference + 5.4%; $p<0.003$ Table 3). Similar

Table 3: Pooled mean prevalence of resistance to antimicrobial agents among select isolates from patients treated in intensive care units (ICUs)

Antimicrobial resistant organisms	No. of ICUs	Pooled mean,% (No. experimental) IBRS	Pooled mean,% (No. experimental) LBRS	Pairwise difference (%) Mean	Pairwise difference (%) p-value
Quinolone resistant *E. coli*	10	41.2	33.8	5.4	0.003
Methicillin-resistant coagulase N. staphylo	14	19.1	17.9	1.5	0.41
Cefazidine-resistant *E. coli*	20	24.6	71.6	7.1	0.005
Quinolone resistant *E.coli*	16	25.3	7.8	0.2	0.41
Cefepime resistant *Citrobacter freundii* (-)	16	20.8	4.2	0.6	0.40
	15	15.1	25.4	0.0	0.36
Ciprofloxacin resistant *Klebsiella pneumoniae*	10	28.5	15.3	3.7	0.51
Gentamycin-resistant *Neisseria meningitidis*	13	4.9	11.5	3.1	0.47
Amoxyclav-resistant *S. pneumoniae*	10	15.1	23.7	1.6	0.50
Quinoxy resistant *P. aernginosa*	25	17.3	14.3	0.8	0.63
Piperacilllin-resistant *P. aeruginosa*	25	12.0	16.5	2.6	0.89

comparisons for the other orgamisms evaluated identified no additional significant differences. Similar analysis comparing the percentage of isolates susceptible to the antimicrobial revealed similar results. It was noted that the mean difference in the prevalence of vancomycin-susceptible enterococci between the 2 systems was 11%, although this difference still did not reach statistical significance.

DISCUSSION

Antibiograms are often taken into account to define a rational selection of an empirical antimicrobial therapy for treating patients with hospital acquired selection between the antibiogram constructed with laboratory based data and that formed with subjected data by prior to clinical validation (Critchley and Karlowsky, 2004). Although antibiograms are used for multiple purposes, one of their most common uses is to assist clinicians in the design of empirical therapies for suspected infections within a hospital setting. Surprisingly Critchley and Karlowsky (2004) recommended the reliability of antibiograms to be used for this purpose has rarely been assessed. Fridkin *et al*. (2003) in addition, to better aid in empirical therapy decisions for hospitalized patients; separate summary reports would be needed for hospital-and community-acquired infections. Such reports would be difficult to generate for many clinical microbiology laboratories. Aggregating cumulative susceptibility data is a common practice among clinical microbiology laboratories but the best methodology to analyze and present these data has not been determined. The most common use of the hospital antibiograms data is probably for assisting clinicians with empiric therapy for suspected infections (Enzensberger *et al*., 2005). Furthermore, Khanfar *et al*. (2009) evaluated the preserving efficacy for different cough syrups manufactured by different pharmaceutical companies also explained the preservatives mixtures of propylene glycol with glycerol or with glycerin or with butyl paraben preservatives as well as methyl paraben with probyl paraben are acceptable clinically and have considerably antimicrobial activity against infectious bacteria during the 48 h studied period.

Previously, Highley *et al*. (2006) and Rouini *et al*. (2006) reported that the variety of antibiotics suitable for the different acute diseases in human, they also investigated the pharmacokinetics of mitomycin C when administered with ifosfamide and cisplatin as part of the mitomycin C, ifosfamide and cisplatin (MIC) regimen and recently updated on pharmacology by Zhou *et al*. (2008) and Momtaz and Abdollahi (2010). Very recently, Shakyawar *et al*. (2011) described about target the potential drug used for the various ascitic fluid based diseases followed by Hollowell *et al*. (2002) and Gharaei-Fathabad (2011) explained the antibiogram level studies in pharmacology industries.

This study suggests cumulative susceptibility data (laboratory-based reporting) that clinicians use to guide empiric treatment of hospital-acquired infections usually will be representative of the organisms frequently encountered among hospital-acquired infections. This study evaluated select patterns of resistance to antimicrobial agents among the organisms most frequently associated with hospital-acquired infections and compared the resistance rates reported to a laboratory-based monitoring system (NIS-ICARE) to rates reported to an infection-based monitoring system (NIS-ICU). With four exceptions, the resistant rates among the isolates associated with only hospital-acquired infections were similar to rates among isolates associated with infection (both community and hospital acquired), colonization and contaminants.

Mainly two organisms associated with significantly higher rates of resistance among isolates reported to the infection-based system compared with the laboratory-based system were MRSA and methicillin-resistant coagulase-negative staphylococci. Although several other organisms tended to be associated with higher resistance rates in the

infection-based system, these differences were not statistically significant. Second, patients with longer hospital stays are at increased risk to become infected with antimicrobial-resistant pathogens and these isolates would be more represented in a infection-based system (i.e., nosocomial infection) than the laboratory-based system (Gold and Moellering, 1996; Rice *et al*., 1996). Third, there would be potential for reporting bias if infection control practitioners were more likely to report hospital-acquired infections when they were associated with an antimicrobial-resistant pathogen, although this seems unlikely (Stewarda *et al*., 2000; Vijayakumar *et al*., 2010). Some of these hypotheses may explain the significantly higher resistance rates observed in data from infection-based reporting compared with that from laboratory-based reporting among MRSA and methicillin-resistant coagulase-negative staphylococci. However, the impact of these factors does not appear strong enough to consistently create differences in measured resistance prevalence of any magnitude worthy of clinical importance (Frank *et al*., 1999; Jones, 2003). However, the relative differences in resistance prevalence observed were small (<10%) and unlikely to have any clinical impact, even if differences were to become statistically significant.

The major differences between these patient groups in terms of resistance to antimicrobial agents are higher severity of illness and higher rates of resistance to antimicrobial agents. A second limitation of this study shows the exclusion of many ICUs from some analysis because <10 isolates of a particular organism had been reported to NNIS-ICU during the study period. Furthermore, Bantar *et al*. (2000) and Shlaes *et al*. (1997), in order to that the Society for Healthcare Epidemiology of America and Infectious Diseases Society of America Joint Committee provided the guidelines for the preventions of antimicrobial resistance in hospitals on the prevention of antimicrobial resistance. This may be reflect a very low hospital-acquired infection rate overall or a paucity of infections caused by the particular organism under study. Finally, this hypothesis was tested correlated with explained only selected organisms and may not hold true for the less frequently encountered pathogens. Though Singh *et al*. (2003) also explained comparisons of resistance prevalence among other pathogens of clinical concern (i.e., *Actinobacter* species, *S. pneumoniae*) may not show similar results to this study. For example, others have reported that infections with MRSA that arise outside of the hospital setting (i.e., community-onset MRSA) are frequently associated with MRSA that is susceptible to clindamycin. These limitations do not detract from the observations that differences between reporting systems were small and not clinically relevant and mostly insignificant (Carroll *et al*., 2000). Analysis of these data supports the aggregation of cumulative susceptibility data from both hospital-acquired infections and other isolates which may include isolates from community-acquired infections, colonization or contaminants, into one summary report for use in guiding empiric therapy in hospitalized patients (Fridkin *et al*., 2003; Zapantis *et al*., 2005b). From this study showed the concept also agreed with other findings by Jones (2003). Though, few researchers had been them contradictory view proposed by Critchley and Karlowsky (2004) and Arab *et al*. (2006) mainly because all the hospital patients affected by number of diseases so the particular types of antibiotics doesn't activated clinicians should be aware that the MRSA and methicillin-resistant coagulase-negative staphylococci prevalence rates presented in such summary tables may under represent to a small degree their actual prevalence among pathogens associated with hospital-acquired infections (Goldmann *et al*., 1996; Jones, 2003). The small magnitude of this difference means that it should rarely affect decisions about drug choice. Therefore, producing one summary report should provide useful relevant data to the clinician and minimize the need for additional efforts to produce more detailed reports on subgroups. However, in some settings, reporting of separate cumulative susceptibility data from ICU areas combined may be useful to clinicians (Bantar *et al*., 2007). Likewise, separate reports for specific patient populations (e.g., patients undergoing dialysis or patients with cystic fibrosis) may be helpful as well.

CONCLUSION

From this study concluded the laboratory-based data underestimate the frequency of several major resistant organisms in patients with hospital-acquired infection. Previous clinical validation of the individual susceptibility reports seems to be a suitable strategy to get more reliable data. The resistant rates among the isolates associated with only hospital-acquired infections were similar to rates among isolates associated with infection (both community and hospital acquired), colonization and contaminants.

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