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RESEARCH

COMPARISON RESULTS OF ANALYTICAL PROFILE INDEX AND DISC DIFFUSION ANTIMICROBIAL SUSCEPTIBILITY TEST TO TECHNICAL DEDICATED REASONABLE 300B METHOD

(Perbandingan Hasil Analytical Profile Index dan Uji Kepekaan Antibiotika Difusi Cakram dengan Metode Technical Dedicated Reasonable 300B)

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ABSTRAK

Angka kematian infeksi aliran darah cukup tinggi, berkisar 20–50%. Patogen penyebab dapat dibuktikan dengan pemeriksaan kultur darah yang dilanjutkan dengan uji kepekaan antibiotika. Metode pemeriksaan dapat dilakukan secara manual atau automatis baik semiautomatis ataupun automatis penuh. Metode manual relatif tidak memerlukan biaya yang besar dibandingkan metode automatisasi. Penelitian ini merupakan analisis observasional dengan desain potong lintang. Metode identifikasi manual memakai metode API dan uji kepekaan antibiotika metode difusi cakram antibiotika Kirby Bauer. Kedua metode ini dibandingkan dengan metode semiautomatis TDR-300B. Metode automatis penuh VITEK 2 digunakan sebagai metode rujukan untuk menilai kinerja metode konvensional dan semiautomatis. Bakteri penyebab infeksi aliran darah didominasi Gram negatif kebanyakan Eschericia coli dan Klebsiella pneumonia. Ketepatan metode identifikasi API terhadap VITEK 2 sebesar 87,87%, ketepatan identifikasi metode TDR-300B terhadap metode VITEK 2 adalah 90,9%. Hasil ketepatan uji kepekaan antibiotika metode konvensional difusi cakram antibiotika Kirby Bauer terhadap metode VITEK 2 adalah 84,64%. Ketepatan uji kepekaan antibiotika metode TDR-300B terhadap metode VITEK 2 sebesar 82,5%. Ketepatan metode API terhadap metode TDR-300B sebesar 84,84%. Ketepatan uji kepekaan antibiotika metode konvensional terhadap metode TDR-300B sebesar 78,21%. Hasil metode identifikasi dan uji kepekaan antibiotika konvensional tidak berbeda bermakna secara statistik dengan metode semiautomatis TDR-300B. Metode identifikasi dan uji kepekaan antibiotika konvensional masih dapat dipercaya terutama untuk daerah dengan keterbatasan biaya atau pemeriksaan masih sedikit.

Kata kunci: *Perbandingan, API, difusi cakram, TDR-300B*

ABSTRACT

The bloodstream infection death rate is quite high, ranging from 20% to 50%. Causable pathogens could be demonstrated by blood cultures followed by antimicrobial susceptibility tests. The test could be performed in a manual, semiautomatic or fully automatic method. The manual method does not require large investment costs compared to automatic methods. This was an observational cross sectional design study. Manual identification method used API and antimicrobial susceptibility tests used disc diffusion method of Kirby Bauer. Both methods were compared to semiautomatic TDR-300B method. A fully automatic VITEK 2 method was used as the reference method for assessing the performance of manual and semiautomatic methods. Bacteria that caused bloodstream infections were mostly dominated by Gram-negative *Escherichia coli* and *Klebsiella pneumonia*. The accuracy of API identification method to the VITEK 2 was 87.87%, accuracy of TDR-300B identification method to VITEK 2 method was 90.9%. The accuracy results of manual Kirby Bauer disc diffusion antimicrobial susceptibility tests method compared to VITEK 2 method was 84.64%. Accuracy of TDR-300B antimicrobial susceptibility tests method to VITEK 2 was 82.5%. The accuracy of API identification method to TDR-300B was 84.84%.The accuracy of manual antimicrobial susceptibility test method to TDR-300B was 78.21%. The results of manual identification and antimicrobial sensitivity tests were not statistically significanly different with semiautomatic TDR-300B method. Manual identification and antimicrobial susceptibility test methods could be trusted, especially for financial limited region or small number of examination.

Key words: Comparison, API, disc diffusion, TDR-300B

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INTRODUCTION

Normal blood is sterile. The presence of bacteria in the blood stream which is known as bacteremia usually has a pathological nature. The entry of bacteria into bloodstream can cause serious problems including shock, organ failure, Disseminated Intravascular Coagulation (DIC) and death. The World Health Organization (WHO) data in 2001 showed that the mortality reached 85% in some cases of infection worldwide.[1] Infectious diseases cause the death of two million people in India every year.[2] The mortality rate in bloodstream infections ranges between 20–50%.[3] Bloodstream infections in Jakarta according to the Indonesian Department of Health reach about 26.4%.[4] Blood cultures are done to identify the bacteria or other microorganisms in the blood, followed by antimicrobial sensitivity testing to determine the appropriate antibiotics.[5]

Identification methods and antimicrobial sensitivity tests are grouped into genotypic and phenotypic examination methods. The phenotypic method is the most commonly used method. It is usually done through manual or automated methods. The manual identification method is done through biochemical testing either manually or with commercial media such as the Analytical Profile Index (API). Manual antimicrobial sensitivity tests are performed by disc diffusion or dilution method. Automation in bacterial identification and antimicrobial sensitivity tests method are divided into semiautomatic, for example, Technical Dedicated Reasonable (TDR)-300B method and fully automatic methods such as VITEK 2.[3,6–11]

Manual identification and antimicrobial sensitivity test methods do not require analytical equipment that cost billions of rupiahs. Thus, this method is more likely to be used in areas with limited financial source or low workload compared to that of automatic or genotype method. This method may require more trained human resources to make the media, but it can be reduced by using commercial media like API. Analytical profile index methods of Biomerieux constitute one of the manual commercial methods of widely used since 1971. Analytical profile index method is limited for microorganism identification through 20 biochemical tests, so that the antibiotic sensitivity tests further use another method.[6,7] The accuracy of manual methods API to bacterial control varies in some studies around 77–94.6%.[2,7]

Comparison between the manual method, (API and disc diffusion of Kirby Bauer) and semiautomatic method, (TDR-300B) and automatic (VITEK 2), aimed to determine the performance of manual methods whether they can be trusted or have to use automatic methods either semiautomatic or fully automatic one. This comparison is expected to provide input when using manual method in limited financial condition or slightly examinations. Comparison of these two methods has never been studied before. Automatic VITEK 2 method having a better accuracy (range 97.8% to 98.02%) was used as a reference method to see the performance of manual and semiautomatic methods in this study.[2,7]

METHODS

This study was a cross-sectional observational study. It has been approved by the ethics committee of the Dr. Soetomo Hospital Surabaya. The samples were bacterial isolates taken from blood culture of patients with blood stream infections in the Dr. Soetomo Hospital, Surabaya. These were 33 samples taken from several wards. Bacterial isolates were identified by API methods of Biomerieux, semiautomatic TDR-300B (Mindray) and automatic VITEK 2 (Biomerieux). Analytical profile index examination was then continued with manual antimicrobial sensitivity test using Kirby Bauer agar diffusion method. Examination of the manual, semiautomatic and automatic methods were performed in three different laboratories. Analytical profile index method was a microorganism identification test using 20 biochemical tests. Dried biochemical substances were packed in a minitube, then bacterial suspension was inoculated into the minitube and incubated. The positive or negative result reaction was adjusted to the reference value of the API Web to determine the bacterial strain.[13–16]

Semiautomatic TDR-300B method used several separate devices and inserting specimen into each device was done manually. Bacterial suspension turbidity level was read by TDR-Z200 microbe turbidimeter then inoculated into the reagent card by TDR-J100 automated dosing system. Each card contains biochemical reagents for identification test and antibiotics for sensitivity test. Reagent card containing bacterial suspension was incubated then read by of TDR-300B microorganism analysis system.[24] Automatic VITEK 2 method was a fully automated instrument in which incubation, identification analysis of microorganism and antimicrobial sensitivity tests were performed on the same device (inserting specimen, inoculator, incubator and microorganism analysis system in one device)[24] so it does not require any other device as TDR-300B method. Bacterial suspension was inoculated into the appropriate card in TDR-300B and

Vitek 2 methods. The identification and antimicrobial sensitivity tests were analyzed automatically both in TDR-300B and Vitek 2 methods.[7]

RESULTS AND DISCUSSION

Quality control in this study was done first by examination of bacterial control strain (*Staphylococcus aureus* ATCC 29213, *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853) by API, disc diffusion of Kirby Bauer, TDR 300-B and VITEK 2. The results matched in all methods. Samples comprised a number of 109 patients, obtained from some wards such as Intensive Care Unit (ICU), Emergency room and Surgery Ward. Blood was inserted into the TDR Aerobic Culture tube. It was found that 61 samples (55.96%) showed no growth of microorganism and 48 samples (44.03%) showed growth. The bacteria grew in 33 samples (30.27%), the remaining 15 samples (13.7%) were fungal infections. Patients with bloodstream infections consisted of 14 (42.42%) males and 19 (57.57%) females. The age ranged from 21 to 93 years old. Bacteria that cause blood stream infections consisted of 5 (15.15%) Gram-positive and 28 (84.84%) Gram-negative.

Based on the Vitek 2, distribution of infection causing bacteria strain consisted of *Escherichia coli* (45.45%), *Klebsiella pneumoniae* (18.18%), *Acinetobacter baumannii* (9.09%), *Staphylococcus aureus* (9.09%), *Enterobacter cloacae* (3.03%), *Staphylococcus hominis* (3.03%), *Pseudomonas aeroginosa* (3.03%), *Proteus mirabilis* (3.03%), *Serratia marcescens* (3.03%) and *Staphylococcus cohnii* (3.03%). Pathogens causing blood stream infection most commonly were caused by Gram-negative bacteria which were dominated by *Escherichia coli* and *Klebsiella pneumonia*. Hoenigl *et al.*[17] stated that *Escherichia coli* was the most frequently cause of bloodstream infection. Qureshi *et al.*[18], also stated that the microorganism isolates most commonly found in blood stream infections were dominated by Gram-negative *Escherichia coli* and *Klebsiella pneumonia*.[17,18]

Analytical profile index method could identify 29 similar bacteria in the VITEK 2, thus the accuracy of the API identification method to VITEK 2 method was 87.87%. TDR-300B method could identify 30 of the same bacteria to VITEK 2 method, so the accuracy of TDR-300B identification method in VITEK 2 amounted to 90.9% (Table 1). Analytical profile index method identified 28 of the same bacteria in the TDR-300B method, thus the accuracy of the API identification method in TDR-300B was 84.84% (Table 2). Statistical analysis of the comparison result on bacteria identification between API and TDR-300B using Mc Nemar Change Test showed a significant value of 1.000 ($p<0.05$). It meant that there was no difference between API bacterial identification results and TDR-300B.

Most samples showed no bacterial growth in the TDR Aerobic Culture medium. Possible causes of no growth bacteria in suspected bloodstream infection patients could be affected by various factors. Antibiotic therapy before blood sampling for culture could lead to false negative results. The discrepancy between media used and bloodstream infection-causing bacteria, e g anaerobic or fastidious bacteria using TDR Aerobic Culture media could be a contributing factor.[19,20]

Table 1. Comparison of API and TDR-300B identification method to VITEK 2 method

Vitex 2 Identification (Number)	API Identification		TDR Identification	
	Matched	Not Matched	Matched	Not Matched
Escherichia coli (15)	14	1 (*Enterobacter cloacae*)	15	–
Klebsiella pneumonia (6)	5	1 (*Enterobacter aerogenes*)	5	1 (*Enterobacter cloacae*)
Acinetobacter baumanii (3)	2	1 (*Enterobacter cloacae*)	2	1 (*Stretophomonas maltophilia*)
Staphylococcus aureus (3)	3	–	3	–
Enterobacter cloacae (1)	1	–	1	–
Staphylococcus hominis (1)	1	–	1	–
Pseudomonas aeruginosa (1)	1	–	1	–
Proteus mirabilis (1)	1	–	1	–
Serratia marcescens (1)	1	–	1	–
Staphylococcus cohnii (1)	–	1(*Staphylococcus aureus*)	–	1 (*Staphylococcus xylosus*)
TOTAL (33)	29	4	30	3
Accuracy	87.87%		90.9%	

Table 2. Comparison of API manual identification to TDR-300B method

API identification	TDR identification	
	Matched	Not matched
Escherichia coli (14)	14	–
Klebsiella pneumonia (5)	5	–
Staphylococcus aureus (4)	3	1(*Staphylococcus xylosus*)
Acinetobacter baumanii (2)	1	1(*Stretophomonas maltophilia*)
Enterobacter cloacae (3)	1	1(*Escherichia coli*) dan 1(*Acinetobacter baumanii*)
Staphylococcus hominis (1)	1	–
Pseudomonas aeruginosa (1)	1	–
Proteus mirabilis (1)	1	–
Serratia marcescens (1)	1	–
Enterobacter aerogenes (1)	–	1(*Enterobacter cloacae*)
Total (33)	28	5
Persentase	84.84%	15.15%

Some composition of substrate used in API and TDR-300B methods were similar but different in working technique and reading results. Turbidity of bacterial suspension on API method that was read by the naked eye through matching to a standard, might not correspond to the recommended level which could cause no optimal substrate reaction. The possibility of errors in viewing the colour change of substrate reaction in API method would be greater than TDR-300B method. It was difficult to determine whether the positive or negative reaction (e.g. differentiate pale red and red, pale blue and blue).[13–16,23–28]

Misidentification of API method was found in Enterobactericeae (*Escherichia coli* and *Klebsiella pneumoniae*). They were identified as *Enterobacter cloacae* and *Enterobacter aerogenes*. O'Hara *et al.*[29] also stated a lower accuracy of Enterobacteriaceae identification (87.7%) on 24 hours incubation. It required additional biochemical tests and incubation to increase the accuracy up to 95.2%.[29] Misidentification might be caused by misinterpretation of biochemical tests. The possibility of misinterpretation of biochemical test on *Escherichia coli* above occurred on negative ADH (L-Arginine) test result interpreted as positive, positive CIT (Trinatriumcitrat) interpreted as negative, or negative VP (Natriumpyruvat) interpreted as positive. These resulted identified bacteria as *Enterobacter cloacae.*[14,29]

ODC (L-Ornithin) and URE (Urea) test misidentification may possibly caused misinterpretation of *Klebsiella pneumonia* as *Enterobacter aerogenes*. Positive ODC test result was interpreted as negative and negative URE was interpreted as positive. Misidentification of *Acinetobacter baumannii* was identified as *Enterobacter cloacae* probably due to misinterpretation of ONPG (2 Nitrophenyl ßD Galactopyranoside), LDC (L-Lysine), ODC (L-Ornithin), VP (Natriumpyruvate), MAN (D-manitol). Misidentification of *Staphylococcus cohnii* identified as *Staphylococcus aureus* might be caused by a difference in biochemical tests in LAC (D-laktosa), SAC (D-saccharose), NAG (N acethyl glucosamine), ADH (L-Arginine) and URE (Urea).[16]

Misidentification of semiautomatic TDR-300B method was rather difficult to find the cause, due to the limited literature on this method. Almost all TDR-300B identification method were done by the devices, such as determination of bacterial suspension turbidity level, inocculation bacterial suspension to the media by automatic pipetting, the reading of the reaction products on the substrate, and the interpretation of results of identification by the analyzer system. Conditions that could possibly lead to misidentification on TDR-300B method such as, the possibility of polymicrobial. Other misidentification-caused possibility was pipetting error resulting in incompatible volume of the inocculated bacterial suspension. Based on the observations during this study, there was sometimes air bubbles in the tip of the pipetting process or decreasing fluid volume due to the presence of air in the tip.[24,30] It could be the weakness of the TDR 300-B system. Another possibility according to TDR-300B manual operation was the presence of contamination by odd materials that possible affect the absorbance readings of photometer on TDR-300B microorganism analysis system.[31]

The accuracy of identification result between API method was not worse than the TDR-300B semiautomatic method and fully automated VITEK 2 method. The kappa coefficient between the API

Table 3. Statistical test for bacterial identification compatibility by Kappa coefficient

Bacterial Identification Methods	Bacterial Identification Methods		
	VITEK2	API	TDR-300B
VITEK 2	–		
API	Kappa=0.840 p=0.000	–	
TDR-300B	Kappa=0.878 p=0.000	Kappa=0.801 p=0.000	–

The coefficient of kappa (κ) by Landis and Koch (1977) categorized as poor agreement ($\kappa<0.00$), slight agreement ($0.00<\kappa<0.20$), fair agreement ($0.21<\kappa<0.40$), moderate agreement ($0.41<\kappa<0.60$), substantial agreement ($0.61<\kappa<0.80$) and almost perfect agreement ($0.81<\kappa<1.00$)[22]

methods and VITEK 2 0.840 (Table 3), showed an almost perfect agreement between the two methods. Kappa value API methods did not vary much to the kappa value of TDR-300B semiautomatic method (0.878) and statistical tests showed no significant difference between the API manual bacterial identification method in semiautomatic TDR-300B method.[22]

Not all antibiotics that were used could be analysed by the three methods because of different antibiotics selection in the three laboratories. Based on the type of antibiotic used, the accuracy of Trimethoprim-Sulfamethoxazole and Cefoxitin by manual method of Kirby Bauer were the worst (0% and 57.14%). The number of Trimethoprim-Sulfamethoxazole test that could be analyzed was only one so that the percentage mismatch was too high. The best accuracy of antimicrobial sensitivity test by Kirby Bauer manual method to VITEK 2 was found in Ampicillin, Clindamycin, Doxycycline, Erythromycin, Tetracycline and Linezolid (100%). The accuracy of TDR-300B antimicrobial sensitivity test method was low in Erythromycin (60%), Cefoxitin (64.28%) and Piperacilin-Tazobactam (64.28%). The best accuracy of antimicrobial sensitivity test (100%) by TDR-300B was obtained in Oxacyline, Clindamycin, Doxycycline, Tetracycline, Linezolid and Ciprofloxacin (Table 4).

Table 4. Comparison of manual antimicrobial sensitivity test and TDR-300B semiautomatic method results to VITEK 2 automatic method

Antimicrobial (Number)	Manual AST		TDR-300B AST	
	Matched (%)	Not Matched	Matched (%)	Not Matched
Amikacin (28)	24 (85,71)	4	22 (78.57)	6
Ampicilin (24)	24 (100)	–	22 (91.66)	2
Oxacilin (5)	4 (80)	1	5 (100)	–
Cefoxitin (28)	16 (57,14)	12	18 (64.28)	10
Ceftazidime (28)	23 (82,14)	5	22 (78.57)	6
Ceftriaxon (23)	22 (95,65)	1	20 (86.95)	3
Gentamycin (33)	29 (87,87)	4	30 (90.90)	3
Clindamycin (4)	4 (100)	–	4 (100)	–
Doxyciclin (1)	1 (100)	–	1 (100)	–
Erytromycin (5)	5 (100)	–	3 (60)	2
Tetracyclin (2)	2 (100)	–	2 (100)	–
Linezolid (4)	4 (100)	–	4 (100)	–
Levofloxacin (33)	28 (84,84)	5	26 (78.78)	7
Ciprofloxacin (5)	4 (80)	1	5 (100)	–
Meropenem (28)	27 (96,43)	1	27 (96.43)	1
Piperacilin- Tazobactam (28)	20 (71,43)	8	18 (64.28)	10
Trimethoprime-Sulfametoxazol (1)	– (0)	1	1 (100)	–
TOTAL (280)	237	43	231	49
Percentage	84.64%	15.36%	82.5%	17.5%

Table 5. Comparison of manual antimicrobial sensitivity test of Kirby Bauer method to TDR-300B and VITEK 2

Kirby Bauer Manual Method	TDR-300B Method	VITEK 2 Method
Matched	219	237
Not Matched	61	43
Accuracy	78.21%	84.64%

Table 6. Statistical test of antimicrobial sensitivity test (AST) of results by Kappa coefficient

AST Methods	AST Methods		
	VITEK 2	Manual	TDR-300B
VITEK 2	–		
Manual of Kirby Bauer	Kappa=0.716 p=0.000	–	
TDR-300B	Kappa=0.682 p=0.000	Kappa=0.582 p=0.000	–

Accuracy of antimicrobial sensitivity test by Kirby Bauer manual method in automated VITEK 2 was 84.64%, while the accuracy of TDR-300B semiautomatic antimicrobial sensitivity test in the automatic VITEK 2 method was 82.5%. Accuracy of Kirby Bauer manual antimicrobial sensitivity test method in TDR-300B semiautomatic method was 78.21% (Table 4 and 5). Comparison on statistical analysis of Kirby Bauer manual antimicrobial sensitivity test method and the TDR-300B semiautomatic antimicrobial sensitivity test by Wilcoxon Signed Ranks Test showed a significant value of 0.10 ($p>0.05$). It meant that there was no significant difference in antimicrobial sensitivity test results between the two methods.

Manual antimicrobial sensitivity test results could be influenced by many factors especially human errors. Based on the literature, causes of errors might be delaying in the inserting antibiotic disc, temperature lower than 35^0C, media thickness, distance between the discs of antibiotics, improper antibiotic disc storage too long or improperly, damage to the composition of media and zone of diameter measurement error could also lead to misinterpretation of the results of antimicrobial sensitivity test.[3,5] This study tried to reduce the influencing factors by following standard procedure operational and by doing bacterial control strain examination.

The accuracy of TDR-300B semiautomatic antimicrobial sensitivity test method results was 82.5% in the VITEK 2 automatic method. Possible causes found in this study using this method included the possibility of polymicrobial confound test results. Other possibility was pipetting error, so the volume of the inocculated bacterial suspension to dehydrated antibiotics was not appropriate. The presence of air bubbles in the tip or the presence of air in the tip as the previous statement might affect the sensitivity reaction to antibiotics in test. The presence of odd material contamination like the powder of the gloves or dirt, due to bacterial suspension inoculation and the addition of immersion oil were done in open space, could affect the absorbance readings of photometer on TDR-300B Microorganism Analysis System.[24,30]

Kappa coefficient (Table 6) between the manual antimicrobial sensitivity tests of Kirby Bauer disc diffusion and VITEK 2 fully automatic referral method amounting 0.716 indicated a strong agreement between the two methods (substantial agreement). Statistical test between the manual antimicrobial sensitivity test of Kirby Bauer disc diffusion method and TDR-300B semiautomatic method showed no significant difference.[22]

CONCLUSIONS AND SUGGESTIONS

Manual identification and antimicrobial sensitivity test methods are still trustworthy, especially for limited financial region or small number of examination. To avoid polymicrobial isolates bacterial selection tested must be considered. The procedures of a manual method require trained personnel, thus require more intensive staff training. Inocculation of bacteria on the automation methods should consider the possibility of contamination by odd substances that may affect the reading of photometer automated analysis system.

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