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Culture-and nonculture-based antibiotics for complicated soft tissue infections are comparable

Ronald Irwanto*,, Suhendro**, Khie Chen**, and Murdani Abdullah*****

ABSTRACT

*Department of Internal Medicine, Faculty of Medicine, Trisakti University
**Division of Infectious and Tropical Diseases, Department of Internal Medicine, Faculty of Medicine, University of Indonesia
***Division of Gastro-Entero-Hepatology, Department of Internal Medicine, Faculty of Medicine, University of Indonesia

Correspondence
dr. Ronald Irwanto, SpPD, KPTI
Department of Internal Medicine, Faculty of Medicine, Trisakti University
Jl. Kyai Tapa Grogol, Jakarta 11440
Phone:
+6221-5672731
Email:
ronald.irwanto@yahoo.com

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BACKGROUND
Data collected in 2010 from Cipto Mangunkusumo Hospital indicate that complicated skin and soft tissue infections accounted for more than 10% of cases. Etiological diagnoses are based on the findings on bacterial culture and thus evaluation of the effectiveness of bacterial culture becomes a necessity. The purpose of this study was to evaluate the operational effectiveness of bacterial culture for etiological diagnosis of complicated skin and soft tissue infections.

METHODS
This was a historical cohort study using secondary data of patients with complicated skin and soft tissue infections admitted for hospitalization to Cipto Mangunkusumo Hospital, Jakarta from July 2011 to July 2012. The 90 subjects meeting the inclusion and exclusion criteria were divided into 2 groups of 45 patients each. Group 1 comprised patients who received initial antibiotic therapy according to cultural results, while the patients in group 2 received initial antibiotic therapy without reference to cultural results. Successful diagnostic culture was assessed by the absence of therapeutic failure. Therapeutic failure was determined using 3 parameters that had to be fulfilled, viz. absence of antibiotic escalation, repeat operations, and clinical deterioration. The latter parameter was assessed by clinical judgement of the attending physician.

RESULTS
After controlling for confounding variables (age, severity of infection, comorbidity), there was no statistical difference in therapeutic success between culture-based and non-culture based initial antibiotic therapies (OR=0.45, p=0.085).

CONCLUSION
This study demonstrates the ineffectiveness of bacterial culture as a diagnostic criterion for appropriate antibiotic therapy of complicated skin and soft tissue infections.

Key words : Culture, antibiotic, diagnostic, skin and soft tissue infection, complicated

Pengobatan antibiotika sesuai dan tidak sesuai kultur pada infeksi jaringan lunak komplikata adalah sebanding

ABSTRAK

LATAR BELAKANG

Data yang diperoleh di ruang rawat inap penyakit dalam Rumah Sakit Cipto Mangunkusumo menunjukkan lebih dari 10% kasus infeksi kulit dan jaringan lunak komplikata sepanjang tahun 2010. Diagnostik kausatif penyebab infeksi ditegakkan melalui temuan kultur, oleh karenanya sangatlah penting untuk menilai efektifitas kultur. Tujuan penelitian ini adalah untuk menilai efektifitas operasional kultur sebagai media diagnostik kausatif pada infeksi kulit dan jaringan lunak komplikata.

METODE

Penelitian merupakan studi historical cohort *menggunakan data sekunder pada pasien-pasien dengan infeksi kulit dan jaringan lunak komplikata yang masuk ke rawat inap penyakit dalam di Rumah Sakit Cipto Mangunkusumo Jakarta antara bulan Juli 2011 - Juli 2012 . Sebanyak 90 subjek yang memenuhi kriteria inklusi dan eksklusi, dibagi dalam 2 kelompok, yaitu kelompok yang diberikan antibiotik awal sesuai kultur tidak sesuai kultur, dengan jumlah 45 subjek untuk masing-masing kelompok. Keberhasilan diagnostik kultur dilihat dari ada tidaknya kegagalan antibiotik yang penilaiannya dilakukan menggunakan 3 parameter yang semuanya harus dipenuhi, yaitu tidak adanya eskalasi antibiotik, tidak adanya operasi ulang, dan tidak adanya perburukan klinis dinilai melalui* clinical judgement *oleh dokter yang merawatnya.*

HASIL

Setelah mengontrol variabel perancu usia, beratnya infeksi dan komorbid, secara statistik tidak ada perbedaan keberhasilan antara antibiotik awal yang diberikan sesuai kultur dengan antibiotik awal yang diberikan tidak sesuai kultur (OR=0,45, p=0,085).

KESIMPULAN

Studi ini menunjukkan pemeriksaan kultur untuk diagnostik penggunaan antibiotik yang sesuai untuk pengobatan infeksi kulit dan jaringan lunak komplikata tidak efektif.

Kata kunci : *Kultur, antibiotik, diagnostik, infeksi kulit dan jaringan lunak, komplikata*

INTRODUCTION

Data collected in 2010 from the internal diseases ward of Cipto Mangunkusumo Hospital indicate that complicated skin and soft tissue infections accounted for more than 10% of cases. Similarly, cases of sepsis also amounted to around 10%. Several studies showed that 4.3%-10.5% of cases hospitalized for sepsis were due to skin and soft tissue infections.[1,2] The high prevalence of infections results in correspondingly high antibiotic usage.[3] This impacts on increased prevalence of bacterial antibiotic resistance, ultimately leading to significant increases in morbidity and mortality.

Marwick et al.[4] in a study on patients at Ninewells Hospital in Scotland found that empirical administration of antibiotics according to UK guidelines failed to significantly reduce patient morbidity. This was presumably caused by inappropriate empirical antibiotic administration with regard to the bacteria causing the infections. The UK guidelines have recorded that inappropriate antibiotic usage in

patients with complicated skin and soft tissue infections resulted in a 20% higher morbidity rate in comparison with patients receiving appropriate antibiotic therapy.[5,6] There is a need for the evaluation of the effectiveness of bacterial-culture-based etiological diagnosis, since in fact antibiotic administration based on bacterial cultural results does not completely guarantee a reduction in patient morbidity and mortality, made possible by the multiplicity of errors in the collection of specimens and reporting of the results. In contrast, administration of antibiotics that is at variance with cultural findings may frequently yield substantial clinical improvement. This is connected with a variety of factors, such as development of bacterial colonization or inappropriate specimen collection methods. The purpose of the present study was to evaluate the effect of culture- and non-culture-based antibiotic administration on the success rate of treatment of complicated skin and soft tissue infections.

METHODS

Research design

This was a historical cohort study using secondary data from the medical records of the internal disease ward of Cipto Mangunkusumo Hospital for the period of July 2011 - July 2012.

Study subjects

Patients admitted to the internal disease ward with complicated skin and soft tissue infection and a variety of clinical manifestations were recruited into this study, with as inclusion criterion completeness of data, including data on bacterial culture. Exclusion criteria were: patients with complicated skin and soft tissue infection referred from other hospitals, who had received antibiotics prior to transfer to Cipto Mangunkusumo Hospital; patients with complicated skin and soft tissue infection showing severe focal infection at other sites; patients from whom pus had been collected after 7 days of hospitalization; and patients with polymicrobial cultures and variable resistance to the administered antibiotic. The sample size was calculated by means of the formula for a difference between 2 proportions, yielding 90 patients meeting the inclusion and exlusion criteria, who were divided into 2 groups of 45 patients each. Group 1 comprised patients who received initial antibiotic therapy according to cultural results, while the patients in group 2 received initial antibiotic therapy without reference to cultural results.

Data collection

Confounding components that were considered to affect host responses to infection were age, disease severity (based on the presence or absence of systemic involvement or sepsis), and comorbidity, such as diabetes mellitus, malignancy, HIV/AIDS, and autoimmune disease, according to the clinical diagnosis of the attending physician.

Assessment of cultural effectiveness

Therapeutic success was determined from the absence of antibiotic failure, using three parameters that had to be fulfilled, viz. absence of antibiotic escalation to indicate antibiotic failure and defined as the administration of antibiotics with increasingly broader spectra, repeat operations, and clinical deterioration. The latter parameter was assessed by clinical judgement of the attending physician.

Statistical analysis

A simple logistic regression was used to determine success of culture- and nonculture-based treatments. Multivariate logistic regression was used to control for confounding variables. All analyses were performed using SPSS for Windows version 15.0.

Research ethics

This study was approved by the Medical Ethics Commission, Faculty of Medicine, University of Indonesia.

Table 1. Clinical characteristics of study subjects based on therapeutic success

Clinical characteristic	Therapeutic success		OR (95% CI)	p
	Yes (n=59)	No (n=31)		
Age				
Older person	18	8	1.26 (0.48-3.35)	0.640
Younger person	41	23		
Gender				
Male	32	19	0.75 (0.31-1.82)	0.521
Female	27	12		
Diabetes mellitus				
Yes	44	19	1.85 (0.73-4.70)	0.191
No	15	12		
Sepsis				
Yes	9	12	0.29 (0.10-0.78)	0.012
No	50	19		
Malignancy				
Yes	10	5	1.06 (0.33-3.43)	0.921
No	49	26		
Decubitus				
Yes	1	2	0.25 (0.02-2.87)	0.272
No	58	29		
Autoimmune disease				
Yes	3	2	0.77 (1.23-4.91)	1.00
No	56	29		
HIV				
Yes	1	1	0.52 (0.52-8.56)	1.00
No	58	30		
Antibiotics				
Culture-based	26	19	0.50 (0.20-1.21)	0.120
Nonculture-based	33	12		

RESULTS

In this study data from 90 patient records were collected. With regard to gender. there were 51 male subjects (56.7%) and 39 female subjects (43.3%). According to age, the younger person group comprised 27 subjects (30.0%). The number of subjects categorized as older person comprised 26 subjects (28.9%). Subjects with diabetic comorbidity were 63 in number. while those with nondiabetic comorbidity comprised 27 subjects. The most frequent cause of nondiabetic comorbidity among the study subjects was malignancy, found in 15 out of 27 subjects (55.6%). There were no differences of clinical characteristic between the two groups expect for sepsis (Table 1). Confounding factors were considered significant at $p<0.25$.

A variety of microorganisms were found upon culture of swabs taken from lesions. Among the microorganisms found on culture, Gram-negative bacteria were the dominant group. Overall, *Pseudomonas* sp were the most numerous, being found in 22 cultures (19.5%), followed by *Escherichia coli* in 20 cultures (17.7%) and *Klebsiella pneumoniae* in 17 cultures (15.0%). Gram-positive bacteria comprised *Staphylococcus aureus* and *Staphylococcus epidermidis*, found in equal numbers, namely in 13 cultures (11.5%) each.

Gram-negative bacteria found in appreciable numbers were *Acinetobacter* sp., present in 10 cultures (8.8%), whereas the microorganism found in lowest numbers in cultures was *Stenothrophomonas maltophilia*, present in 1 culture (0.9%).

Table 2. Patterns of antibiotic sensitivity and resistance of Gram-positive bacteria

Antibiotics	*S.epidermis* (n=13)			*S.aureus* (n=13)		
	R* (n.%)	S@ (n.%)	I# (n.%)	R* (n.%)	S@ (n.%)	I# (n.%)
Oxacilin	7 (53.8)	6 (46.2)	0 (0.0)	2 (15.4)	11 (84.6)	0 (0.0)
Ampicillin	11 (84.6)	2 (15.4)	0 (0.0)	11 (84.6)	2 (15.4)	0 (0.0)
Ampicillin sulbactam	5 (38.5)	7 (53.8)	1 (7.5)	2 (15.4)	11 (84.6)	0 (0.0)
Amoxyllin + clavulinic acid	6 (46.2)	7 (53.8)	0 (0.0)	2 (15.4)	11 (84.6)	0 (0.0)
Cephalotin	6 (46.2)	6 (46.2)	1 (7.6)	0 (0.0)	0 (0.0)	0 (0.0)
Ceftriaxone	7 (53.8)	5 (38.5)	1 (7.7)	2 (15.4)	9 (69.2)	2 (15.4)
Ceftazidine	8 (61.5)	4 (30.8)	1 (7.7)	2 (15.4)	7 (53.8)	4 (30.8)
Cefoperazone	7 (53.8)	2 (15.4)	4 (30.8)	2 (15.4)	6 (46.2)	5 (38.5)
Cefepime	6 (46.2)	6 (46.2)	1 (7.7)	3 (23.1)	10 (76.9)	0 (0.0)
Levofloxacin	8 (61.5)	5 (38.5)	0 (0.0)	8 (61.5)	5 (38.5)	0 (0.0)
Piperacillin-tazobactam	5 (38.5)	5 (38.5)	3 (23.1)	4 (30.8)	6 (46.2)	3 (23.0)
Meropenem	8 (61.5)	5 (38.5)	0 (0.0)	2 (15.4)	11 (84.6)	0 (0.0)
Inipenam	7 (53.8)	6 (46.2)	0 (0.0)	2 (15.4)	11 (84.6)	0 (0.0)
Vancomycin	0 (0.0)	13 (100.0)	0 (0.0)	0 (0.0)	13 (100.0)	0 (0.0)
Teicoplanin	0 (0.0)	12 (92.3)	1 (7.7)	0 (0.0)	13 (100.0)	0 (0.0)

*R=resistant; @S=sensitive; #I=intermediate

The possibility of a high resistance rate of methycillin resistant *Staphylococcus epidermidis* (MRSE) was supported by the finding of a relatively high resistance rate of *S. epidermidis* against beta-lactam antibiotics, amounting to an overall rate of more than 50%.

In contrast to *S.epidermidis*, in the case of *S. aureus* the proportion of representative isolates of methycillin resistant *Staphylococcus aureus (*MRSA) against beta-lactam antibiotics was not sufficiently high. However, the resistance rate was quite high against levofloxacin, attaining 61.5% (Table 2).

The possibility of a high prevalence of extended spectrum beta-lactamase (ESBL) producers is indicated by the high resistance rate of *E. coli* and *K. pneumoniae* against beta lactam antibiotics. The resistance rate of *E.coli* against cephalotin was up to 70%, while the resistance rate against cefotaxime, ceftriaxone and cefoperazone were 55%, 60% and 60%, respectively. *E. coli* showed a high sensitivity toward aminoglycoside antibiotics, with the sensitivity of *E. coli* for gentamycin and amikacin attaining 60% and 70%, respectively. The highest level of sensitivity of *E. coli* was for the carbapenem antibiotics, the sensitivity for meropenem and imipenem attaining 100%. The resistance rate of *K. pneumonia* against beta-lactam antibiotics was also substantially high. In contrast, this species was highly sensitive for the cephalosporins, with the sensitivity for ceftazidime attaining 64.7%. The sensitivity for aminoglycoside antibiotics was also high, that for amikacin attaining 76.5%. However, the sensitivity for gentamycin was only 47.1%. The sensitivity for meropenem and imipenem was also high, being 94.1% for each of them (Table 3).

The resistance rate of *Pseudomonas* sp against cephalosporins was found to be high, being on average above 50%. The lowest rate of resistance against cephalosporins was shown by cefepime, with a resistance rate of only 27.3% and a sensitivity of 54.5%. A relatively high sensitivity was shown for carbapenems, with a sensitivity for meropenem and imipenem of 68.2% and 72.7%, respectively.

Cultural findings for *Acinetobacter* sp showed an extremely high antibiotic resistance both against beta-lactam antibiotics, anti-betalactamases, aminoglycosides and quinolones, attaining rates of 80%-100%.

Table 3. Antibiotic sensitivity and resistance patterns of Gram-negative bacteria

Antibiotics	*E.coli* (n=20)			*K pneumoniae* (n=17)			*Pseudomonas* sp (n=22)			*Acinetobacter* sp (n=10)		
	R*	S@	I#	R	S	I	R	S	I	R	S	I
Ampicillin sulbactam	55.0	45.0	0.0	58.8	41.2	0.0	81.8	18.2	0.0	80.0	20.0	0.0
Amoxyllin+clavulinic acid	45.0	40.0	15.0	47.1	35.3	17.6	95.5	0.0	4.5	90.0	10.0	0.0
Gentamycin	35.0	60.0	5.0	52.9	47.1	0.0	36.4	54.5	9.1	100.0	0.0	0.0
Amikacin	10.0	70.0	20.0	11.8	76.5	11.8	18.2	68.2	13.6	90.0	10.0	0.0
Cephalotonin	70.0	25.0	5.0	47.1	47.1	5.9	90.9	9.1	0.0	100.0	0.0	0.0
Cefotaxime	55.0	35.0	10.0	41.2	58.8	0.0	63.6	4.5	31.9	100.0	0.0	0.0
Ceftriaxone	60.0	35.0	5.0	41.2	58.8	0.0	59.1	18.2	22.7	100.0	0.0	0.0
Ceftazidine	45.0	50.0	5.0	29.4	64.7	5.9	40.9	50.0	9.1	100.0	0.0	0.0
Cefoperazone	60.0	30.0	10.0	52.9	29.4	17.6	45.5	27.3	27.2	100.0	0.0	0.0
Cefepime	35.0	55.0	10.0	23.5	76.5	0.0	27.3	54.5	18.2	90.0	10.0	0.0
Ciprofloxacin	50.0	35.0	15.0	29.4	52.9	17.6	36.4	45.5	18.1	90.0	0.0	10.0
Levofloxacin	45.0	50.0	5.0	41.2	52.9	5.9	40.9	54.5	4.6	80.0	20.0	0.0
Piperacillin+tazobactam	30.0	50.0	20.0	29.1	29.4	41.2	40.9	50.0	9.1	90.0	10.0	0.0
Meropenam	0.0	100.0	0.0	5.9	94.1	0.0	27.3	68.2	4.5	40.0	60.0	0.0
Imipenam	0.0	100.0	0.0	5.9	94.1	0.0	22.7	72.7	4.6	40.0	50.0	10.0
Tigecydin	-	-	-	-	-	-	-	-	-	30.0	60.0	10.0

*R=resistant; @S=sensitive; #I= intermediate; Values represent percentages

Resistance against meropenem and imipenem was 40% for each, with a sensitivity of up to 60%.

After controlling for confounding factors, the success and failure rates of culture-based initial antibiotic treatment and those of nonculture-based initial antibiotic treatment in complicated skin and soft tissue infections are as shown in Table 4.

In this study, significant confounding factors (at $p<0.25$) were diabetes mellitus and sepsis, with a valid model having the smallest OR (0.01) and the narrowest precision of 0.94 with $p=0.085$ and OR=0.45 (Table 4). Therefore, on the basis of the above calculations, there was no statistically significant difference in success rate between culture-based and nonculture-based initial antibiotic administration.

DISCUSSION

In this study, from the viewpoint of demographic and clinical characteristics, subjects in the age group of 46-55 years were the most numerous in comparison with other age groups. With regard to gender, there were more males (56.7%) than females in this study. The demographic characteristics in our study were similar to those obtained by Moran et al.,[7] where 62% of subjects were male. This was in contrast with a previous study by Irwanto et al. on patients with complicated soft tissue infections in the emergency wards of three

Table 4. Comparison of success and failure rates between culture- and nonculture-based initial antibiotic treatment in complicated skin and soft tissue infections

	Success		Failure		Bivariate		Multivariate	
	n	%	N	%	p	OR (95% CI)	p	Adjusted OR (95% CI)
Antibiotic								
Culture-based	26	57.8	19	42.2	0.120	0.50 (0.20-1.21)	0.085	0.45 (0.18-1.12)
Nonculture-based	33	73.3	12	26.7				

hospitals in Jakarta, in which there were more female than male subjects.[8] This gender difference is presumably due to differing time and location of the studies.

Regarding the results of bacterial culture, there were 74.3% Gram-negative microorganisms among the cultural findings, indicating a predominance of Gram-negative microorganisms among the cultural findings. On this point our study differs from several previous studies, where it was demonstrated that in complicated skin and soft tissue infections the cultural results should be dominated by Gram-positive microorganisms.[9-12]

The resistance rate of *S. epidermidis* against oxacillin was relatively high in our study. As oxacillin is representative of methicillin, this high resistance rate of *S. epidermidis* may be indicative of a high probability of MRSE. This resistance rate is quite significant when compared with the resistance rate of *S. epidermidis* against the penicillins (ampicillin) and cephalosporins, which are on average greater than 50%. Previous studies have shown similar results. In the selection of subjects in the setting of emergency departments, the resistance rate of *S. epidermidis* against both oxacillin and beta-lactams (represented by cefoxitin) was identical (62.5%).[8]

The resistance rate of *S. aureus* against oxacillin was categorized as low, being only 15.4%, or found in only 2 of 13 cultures of *S. aureus*. However, this resistance rate was not in accord with the resistance rate against ampicillin of up to 84.6%. The reason for this discrepancy is unclear.

The findings of Miller et al.[13] in Los Angeles showed a considerably high rate of MRSA isolates. However, these isolates came from subjects with necrotizing fasciitis. Therefore, it may be concluded that the subjects in the Los Angeles study had different clinical characteristics when compared with our subjects.

An indication of ESBL producers is found in the resistance of *E.coli* and *K. pneumoniae* against cephalosporins. The study of Rodriguez-Bano et al.[14] showed a relatively high proportion (65%) of ESBL-producing microorganisms in isolates from urine and blood samples. Petkovsek et al.[15] also state that relatively virulent isolates of *E. coli* are frequently found in skin and soft tissue infections.

The high resistance rate of *Pseudomonas* sp. against beta-lactam antibiotics in this study may presumably be used as an indicator for the presence of a high number of multi drug resistant (MDR) *Pseudomonas*. Gillespie [16] states that the carbapenem group of antibiotics may be used as treatment option for administration to cases of infection by MDR *Pseudomonas* or other Gram-negative bacteria. The present study indeed found that the sensitivity of *Pseudomonas* sp. for carbapenems is still high, with the sensitivity for meropenem and imipenem attaining 68.2% and 72.7%, respectively. Fernandez et al.[17] in an in vivo experiment explains that that ceftobiprole, a fifth-generation cephalosporin that acts by binding to the penicillin binding protein-3 (PBP3), was able to significantly inhibit the growth of *P. aeruginosa*. This opens new perspectives for eradication of infections caused by *P. aeruginosa*.[17,18]

The number of isolates of *Acinetobacter* sp in this study was up to 8.8%, but based on their resistance patterns, the proportion of MDR-panresistant *Acinetobacter* sp. was very high. As a rule MDR-panresistant *Acinetobacter* sp are found among cases of extended care with prolonged application of medical devices. However, in the present study, the high proportion of MDR-panresistant *Acinetobacter* sp was in spite of the fact that one of the exclusion criteria was duration of hospitalization of more than seven days. The possiblity of contamination or colonization acquired in hospital cannot be ruled out. Sebeny et al.[19] found in their study that skin and soft tissue infections from trauma with application of medical devices, were a significant risk factor associated with MDR *Acinetobacter.* A history of trauma accompanied by cellulitis with

edema or vesicles, also indicates a significant probability of *Acinetobacter* as the cause of the infection. However, several studies found that skin and soft tissue infections had a relatively high incidence of MRSA, in comparison with other infections. Therefore, there should be a high degree of suspicion of the presence in the community of a high proportion of MRSA that are resistant to penicillins and cephalosporins.[20-22]

In our study there was no statistical difference in therapeutic success rates between culture-based and nonculture-based initial antibiotic treatments for complicated skin and soft tissue infections. This may have been due to presence of sepsis as a confounding variable affecting the relationship between both types of treatment. The proportion of cases without sepsis was as high as 72.5% in the group of patients with successful therapeutic outcomes, as compared with 27.5% in the groups with therapeutic failures. One of the limitations of this study was its historical cohort design, making the study a retrospective one. Therefore the data collected cannot provide detailed information on patient presentations, approaches to treatment or clinical outcomes.

CONCLUSIONS

In this study, a relatively high antibiotic resistance rate was found among Gram-positive as well as Gram-negative microorganisms. After controlling for confounding factors, culture-based initial antibiotic administration did not yield significant success rates in comparison with nonculture-based initial antibiotic administration.

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