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Constructing Unit-Specific Empiric Treatment Guidelines for Catheter-Related and Primary Bacteremia by Determining the Likelihood of Inadequate Therapy

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Abstract

This study aimed to determine the feasibility of using likelihood of inadequate therapy (LIT), a parameter calculated by using pathogen frequency and in vitro susceptibility for determination of appropriate empiric antibiotic therapy for primary bloodstream infections. Our study demonstrates that LIT may reveal differences in traditional antibiograms.

Traditional antibiograms can assist in selecting empiric antibiotics based on in vitro drug activity.^{1,2} However, such antibiograms are not specific for infections by site or type and often require complex integration of susceptibility data when clinicians choose empiric antibiotics.

Likelihood of inadequate treatment (LIT) is a predictive measure previously described that accounts for pathogen frequency and in vitro susceptibility, translating antibiotic resistance rates into numbers of patients that would be inadequately treated with a given antibiotic based on microbiological data.³ Although used in a pilot study for ventilator-associated pneumonia, the usefulness of LIT has not been studied for determination of optimal empiric antibiotic therapy for other infections or in other healthcare settings.

The primary objective of this study was to determine the feasibility of using LIT for determination of appropriate empiric antibiotics for adult patients with primary bloodstream infections (BSIs) to aid the development of unit-specific guidelines.

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METHODS

We performed a retrospective cohort study of adult patients with primary BSI, as defined by National Healthcare Safety Network (NHSN), between July 1, 2007, and June 31, 2009, in the medical ICU (MICU) and the surgical ICU (SICU).⁴ We included primary polymicrobial and monomicrobial BSIs but excluded secondary BSIs and contaminants. The date of infection was defined as the date of the first positive blood culture. Duplicate blood cultures on the same day were excluded. The study was approved by our institutional review board.

Patients were identified and microbiology and susceptibility data were obtained through queries of hospital databases. Catheter-related BSIs were identified using our infection control database. We collected data on patient demographics, date of positive blood culture, and microbiology and antibiotic susceptibility as per Clinical and Laboratory Standards Institute definitions.⁵

Three different LIT parameters (organism-specific, cumulative, and syndrome-specific) were calculated separately for gram-negative and gram-positive organisms and for each ICU. Organism-specific LIT served as the basic calculation for a given pathogen and antibiotic. It was derived by dividing 100 by the percentage of antibiotic resistance among a group of bacteria in any defined group of patients. For example, if 50% of *Escherichia coli* groups were resistant to cefepime, then the *E. coli*-specific LIT for cefepime is equal to 2 (100/50%). Similar to a “number needed to treat,” this value implies that 2 patients with *E. coli* infection would need to be treated with cefepime for 1 to be inadequately treated. If 100% drug resistance is found for a given antibiotic, the LIT equals 1 (100/100%). For those pathogens with 0% resistance, then a LIT of 100 is arbitrarily assigned and interpreted as 1 of 100 patients would be inappropriately treated with a given antibiotic.

The cumulative LIT was calculated as the sum of organism-specific LITs divided by the total number of pathogens isolated in the unit

$$\frac{\sum[\text{LIT}(E.coli), \text{LIT}(K.pn), \text{LIT}(P.aer) \dots]}{n(\text{GN pathogens})},$$

where “GN” is gram-negative, “*K. pn*” is *K. pneumoniae*, and “*P. aer*” is *P. aeruginosa*.

It reflects the percentage of organisms that would have been inadequately covered by a given antibiotic during the study period. Given the example above, the organism-specific LIT for *E. coli* (2) is added to the organism-specific LITs for each gram-negative organism isolated in the unit (ie, 100 for *Klebsiella pneumoniae* and 100 for *Pseudomonas aeruginosa*). The sum is then divided by the total number of gram-negative organisms (3), equaling a cumulative LIT of 67 ([2 + 100 + 100]/3). This implies that 1 of 67 patients with a gram-negative BSI would be treated inadequately with cefepime in the ICU during the study period.

BSI LIT estimates the probability of inappropriate antibiotic therapy for a given infection. It differs from cumulative BSI by taking into account the frequency of pathogens isolated during the study period. To calculate a syndrome-specific LIT, each organism-specific LIT is multiplied by its frequency as a causative pathogen during the study period. The product for each organism is then summed and divided by the cumulative percentage of all pathogens considered:

$$\frac{\sum[\text{LIT}(E.coli) \times \%fr(E.coli) + \text{LIT}(K.pn) \times \%fr(K.pn) \dots]}{n(\%fr \text{ GN pathogens})},$$

where “% fr” is percentage of frequency, “GN” is gram-negative, and “*K. pn*” is *K. pneumoniae*.

For example, if *E. coli* accounts for 40% of the BSIs during the study period, then *E. coli* treated with cefepime (having had an LIT of 2) is multiplied by 40%, equaling 80. This is repeated for each gram-negative pathogen isolated in the ICU per antibiotic and summed (eg, total of 6,080). The product is then divided by the cumulative percentage of BSI pathogens that were gram-negative in the ICU during the study period (eg, 6,080/100% or BSI LIT of 61). This translates to 1 of 61 patients with a gram-negative BSI would be treated inadequately with cefepime.

RESULTS

Overall, 1,073 blood cultures were identified during the study period. A total of 218 unique pathogens were isolated from 205 subjects; 131 episodes in the MICU and 87 episodes in the SICU were analyzed. Patient demographics are listed in Table 1. Microorganisms and LIT parameters are shown in Table 2 for the MICU and Table 3 for the SICU.

For the MICU, 9 gram-negative pathogens were isolated; the most frequently identified were *K. pneumoniae* and *E. coli*. For *K. pneumoniae*, 0% resistance was found for carbapenems and gentamicin and thus represented by an organism-specific LIT of 100. For tobramycin, ciprofloxacin, and piperacillin-tazobactam, there was 11.1% resistance for each, corresponding to a LIT of 9. Ceftazidime and cefepime had the lowest (worst) organism-specific LIT of 5. Looking at cumulative LIT in the MICU, gentamicin and carbapenems were the best empiric antibiotics.

The BSI LIT was used to determine the rank order of antibiotics most likely to ensure effective empiric therapy against gram-negative pathogens in the MICU: gentamicin and carbapenems were the best, followed by tobramycin, ceftazidime, piperacillin-tazobactam, ciprofloxacin, and cefepime (Table 2).

For gram-positive organisms, *Staphylococcus aureus* was the most commonly isolated pathogen in the MICU (vancomycin LIT of 100). For *Enterococcus faecium* the organism specific LIT was 1 (meaning 100% resistance). Overall, the cumulative LIT for vancomycin was 57, and the BSI LIT was 76.

For the SICU (Table 3), tobramycin and carbapenems ranked best for empiric gram-negative coverage based on BSI LIT. Vancomycin ranked first for gram-positive coverage.

DISCUSSION

Determination of the LIT will help clinicians in selecting an appropriate empiric antibiotic based on type of infection. This study is the first to our knowledge to demonstrate the feasibility and ability of the LIT to determine the probability of inadequate antibiotic therapy for adult ICU patients with primary BSIs.

At our institution, piperacillin-tazobactam is the most commonly prescribed antibiotic for empiric gram-negative coverage, partially due to favorable in vitro activity as reflected in both our hospital-wide and unit-specific antibiograms. However, determination of the LIT

predicted that piperacillin-tazobactam would not have been the most appropriate empiric antibiotic for BSIs in both ICUs. This may be due to the higher rates of piperacillin-tazobactam resistance (as evidenced by lower LITs) in highly prevalent organisms (such as *K. pneumonia* and *E. coli* in the MICU and *Acinetobacter* spp. in the SICU). Thus, the LIT parameter combines microbiologic and epidemiologic data and is an additional decision-support tool for antibiotic selection.

Cumulative LIT and syndrome-specific LIT may differ from each other and between different patient care units. In our study, the rank order of antibiotics for gram-negative organisms differed when comparing the cumulative LIT and BSI LIT in each ICU. This led to a more favorable BSI LIT for tobramycin in the SICU. This observation underscores the importance of factoring in the incidence of pathogens when selecting empiric antibiotic coverage (captured with the syndrome-specific LIT). In contrast, traditional antibiograms do not account for pathogen incidence into syndrome-specific decisions.

For empiric gram-positive coverage, vancomycin had a LIT of 100 for *S. aureus* in both ICUs. In contrast, vancomycin had low LITs for enterococcal BSIs due to high prevalence of vancomycin-resistant enterococcus (VRE) in both units. Such high vancomycin resistance rates among *E. faecium* isolates were surprising. These results added to our current antibiogram data, implying that other agents with activity against VRE may be more appropriate empiric therapy compared to vancomycin for gram-positive infections in our ICUs.

Our study has limitations. First, we separated the LIT calculations by unit, resulting in small numbers of isolates, which can impact LIT calculations. Although extending the study period would have increased these numbers, we felt that a shorter time period would give us a better picture of current resistance rates of microorganism in our units. Our inclusion and exclusion criteria were based on microbiological data; thus, it is possible that some included BSIs represented secondary infections. This issue, however, may be more representative of a “real world” scenario, because the primary source of many BSIs often cannot be determined by culture data.

Our LIT calculations should not be generalized to other units or other hospitals, as the resistance patterns are specific to our institution and the respective ICUs. Finally, patient-specific, drug-specific, and disease-specific factors should be considered when identifying optimal therapy. Because LIT are based on microbiologic data and in vitro susceptibilities, it does not factor in patient-specific data (eg, comorbidities, prior antibiotic therapy, or appropriate antibiotic dose) or patient outcomes; therefore, LIT should be interpreted only in light of such limitations.

Our study demonstrates that determination of LIT can reveal differences in the rank order of appropriate antibiotics for empiric therapy when compared with traditional antibiograms. Additionally, the results of our study underscore the importance of collecting and analyzing unit-specific surveillance information and microbiological data. Such surveillance is essential for antimicrobial stewardship. Our study shows that syndrome-specific LIT (which takes into account prevalence of a pathogen) is important when designing empiric antibiotic regimens. Although LIT calculations are not routinely performed, they may provide a valuable aid to incorporating local microbiological data into the formation of unit-specific guidelines for empiric therapy of disease-specific infections.

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TABLE 1**Patient Demographics by Unit**

Characteristic	MICU	SICU	Total
Patients, no.	123	82	205
BSI pathogens, no.	131	87	218
Age, years, mean $\pm$ SD	63 $\pm$ 15	57 $\pm$ 17	59 $\pm$ 16
Male, no. (%)	66 (53.7)	52 (63.4)	118 (58)
Site of acquisition, no. (%)			
Community onset	76 (61.8)	10 (12.2)	86 (42)
Healthcare-associated, hospital onset	47 (38.2)	72 (87.8)	119 (58)
Catheter-related BSI, no. (%)	8 (6.1)	24 (27.6)	32 (15.6)
Central line	8 (100)	21 (87.5)	29 (90.6)

NOTE. BSI, bloodstream infections; MICU, medical intensive care unit; SICU, surgical intensive care unit; SD, standard deviation.

TABLE 2
Medical ICU Likelihood of Inadequate Therapy (LIT), Cumulative LIT, and Bloodstream Infection (BSI) LIT for Isolated Bacteria

Pathogen	Frequency ^a	LIT ^b (% drug resistance)							BSI LIT								
		GEN	TOB	CIP	PIP/T	CAB	CAZ	CPM	GEN	TOB	CIP	PIP/T	CAB	CAZ	CPM		
GN																	
<i>K. pneumoniae</i>	9 (6.9)	100 (0)	9 (11.1)	9 (11.1)	9 (11.1)	100 (0)	5 (20)	690	62.1	62.1	62.1	690	34.5	34.5			
<i>E. coli</i>	9 (6.9)	100 (0)	100 (0)	2.3 (44.4)	9 (11.1)	100 (0)	100 (0)	690	690	15.9	62.1	690	690	690			
<i>P. aeruginosa</i>	5 (3.8)	2.5 (40)	5 (20)	2.5 (40)	100 (0)	2.5 (40)	5 (20)	9.5	19	9.5	380	9.5	19	19			
<i>E. cloacae</i>	4 (3)	100 (0)	100 (0)	100 (0)	100 (0)	100 (0)	4 (25)	300	300	300	300	300	12	12			
<i>K. oxytoca</i>	4 (3)	100 (0)	100 (0)	100 (0)	2 (50)	100 (0)	4 (25)	300	300	300	6	300	12	12			
<i>S. marcescens</i>	4 (3)	100 (0)	100 (0)	100 (0)	100 (0)	100 (0)	100 (0)	300	300	300	300	300	300	300			
<i>S. maltophilia</i>	2 (1.5)	1 (100)	1 (100)	2 (50)	1 (100)	1 (100)	100 (0)	1.5	1.5	3	1.5	1.5	150	1.5			
<i>M. morganii</i>	1 (0.8)	100 (0)	100 (0)	100 (0)	100 (0)	100 (0)	100 (0)	80	80	80	80	80	80	80			
<i>C. freundii</i>	1 (0.8)	100 (0)	100 (0)	100 (0)	1 (100)	100 (0)	1 (100)	80	80	80	80	80	0.8	0.8			
Total	39 (29.7)	703.5	615	515.8	422	703.5	419	320	2,451	1,832.6	1,150.5	1,192.5	2,451	1,298.3	1,149.8		
Cumulative ^{c,d}		78.2	68.3	57.3	46.9	78.2	46.6	35.6	82.5	61.7	38.7	40.2	82.5	43.7	38.7		
		LIT ^b (% drug resistance)							BSI LIT								
		VAN	AMP	NAF	VAN	AMP	NAF	VAN	AMP	NAF	VAN	AMP	NAF				
GP																	
<i>S. aureus</i>	30 (22.9)	100 (0)	1 (100)	1.9 (53.3)	2,290	22.9	43.5										
<i>E. faecium</i>	13 (9.9)	1 (100)	1 (100)	NT	9.9	9.9	NT										
<i>E. faecalis</i>	10 (7.6)	100 (0)	100 (0)	NT	760	760	NT										
CoNS	10 (7.6)	100 (0)	NT	1.4 (70)	760	NT	10.6										
<i>S. pneumonia</i>	2 (1.5)	NT	NT	NT	NT	NT	NT										
<i>S. viridans</i>	1 (0.8)	NT	NT	NT	NT	NT	NT										
<i>C. striatum</i>	1 (0.8)	100 (0)	NT	NT	80	NT	NT										
Total	67 (51.1)	401	102	3.3	3,899.9	792.8	54.1										
Cumulative ^{e,f}		57.3	14.6	0.5	76.3	15.5	1.1										

NOTE. Data are no. (%) of participants, unless otherwise indicated. AMP, ampicillin; CAB, carbapenems; CAZ, ceftazidime; CIP, ciprofloxacin; CoNS, coagulase negative staphylococci; CPM, cefepime; GEN, gentamicin; GN, gram-negative; GP, gram-positive; ICU, intensive care unit; NAF, nafcillin; NT, not tested; PIP/T, piperacillin-tazobactam; TOB, tobramycin; VAN, vancomycin.

- ^a 131 total BSI pathogens (overall BSI percentage includes 16.2% fungal, 1.5% anaerobic, and 1.5% other).
- ^b LIT = 100/(% drug resistance); 0 drug resistance represents an LIT of 100.
- ^c Cumulative LIT: sum of LITs/no. of GN pathogens studied ($n = 9$).
- ^d BSI LIT: sum of LITs multiplied by percentage of frequency for each organism/cumulative percentage of GN pathogens ($n = 29, 7\%$).
- ^e Cumulative LIT: sum of LITs/no. of GP pathogens studied ($n = 7$).
- ^f BSI LIT: sum of LITs multiplied by percentage of frequency for each organism/cumulative percentage of GP pathogens ($n = 51, 1\%$).

TABLE 3
Surgical ICU Likelihood of Inadequate Therapy (LIT), Cumulative LIT, and Bloodstream Infection (BSI) LIT for Isolated Bacteria

Pathogen	Frequency ^d	LIT ^b (% drug resistance)							BSI LIT								
		GEN	TOB	CIP	PIP/T	CAB	CAZ	CPM	GEN	TOB	CIP	PIP/T	CAB	CAZ	CPM		
		GN															
<i>K. pneumoniae</i>	5 (5.7)	100 (0)	100 (0)	100 (0)	100 (0)	100 (0)	100 (0)	100 (0)	570	570	570	570	570	570	570		
<i>Acinetobacter</i> spp.	5 (5.7)	5 (20)	100 (0)	5 (20)	5 (20)	5 (20)	2.5 (40)	2.5 (40)	28.5	570	28.5	28.5	28.5	14.3	14.3		
<i>E. cloacae</i>	4 (4.6)	100 (0)	100 (0)	100 (0)	100 (0)	100 (0)	100 (0)	100 (0)	460	460	460	460	460	460	460		
<i>P. aeruginosa</i>	4 (4.6)	100 (0)	100 (0)	4 (25)	100 (0)	100 (0)	4 (25)	4 (25)	460	460	18.4	460	460	18.4	18.4		
<i>C. freundii</i>	3 (3.4)	100 (0)	100 (0)	100 (0)	100 (0)	100 (0)	3 (33.3)	100 (0)	340	340	340	340	340	10.2	340		
<i>E. coli</i>	2 (2.3)	2 (50)	2 (50)	1 (100)	2 (50)	100 (0)	2 (50)	2 (50)	4.6	4.6	2.3	4.6	230	4.6	4.6		
<i>S. maltophilia</i>	2 (2.3)	1 (100)	1 (100)	1 (100)	1 (100)	1 (100)	2 (50)	1 (100)	2.3	2.3	2.3	2.3	2.3	4.6	2.3		
<i>E. aerogenes</i>	1 (1.2)	100 (0)	100 (0)	100 (0)	100 (0)	100 (0)	100 (0)	100 (0)	120	120	120	120	120	120	120		
<i>K. oxytoca</i>	1 (1.2)	100 (0)	100 (0)	100 (0)	100 (0)	100 (0)	100 (0)	100 (0)	120	120	120	120	120	120	120		
<i>M. morganii</i>	1 (1.2)	1 (100)	1 (100)	100 (0)	100 (0)	100 (0)	1 (100)	1 (100)	1.2	1.2	120	120	120	1.2	120		
<i>S. marcescens</i>	1 (1.2)	1 (100)	1 (100)	100 (0)	100 (0)	100 (0)	1 (100)	1 (100)	1.2	1.2	120	120	120	1.2	120		
Total	29 (33.4)	610	705	711	808	906	415.5	709.5	21,078	2,649.3	1,901.5	2,345.4	2,570.8	1,324.5	1,889.6		
Cumulative ^{c,d}		55.5	64.1	64.6	73.5	82.4	37.8	64.5	63.1	79.3	56.9	70.2	77	39.7	56.6		
GP		LIT ^b (% drug resistance)							BSI LIT								
		VAN	AMP	NAF	VAN	AMP	NAF	VAN	AMP	NAF	VAN	AMP	NAF				
<i>E. faecium</i>	11 (12.6)	2.7 (36.4)	1.2 (81.8)	NT	34	15.1	NT										
CoNS	11 (12.6)	100 (0)	NT	2 (50)	1,260	NT	25.2										
<i>S. aureus</i>	6 (6.9)	100 (0)	NT	3 (33.3)	690	NT	20.7										
<i>E. faecalis</i>	5 (5.7)	100 (0)	100 (0)	NT	570	570	NT										
<i>E. durans</i>	1 (1.2)	100 (0)	100 (0)	NT	120	120	NT										
<i>S. pneumoniae</i>	1 (1.2)	NT	NT	NT	NT	NT	NT										
<i>S. viridans</i>	1 (1.2)	NT	NT	NT	NT	NT	NT										
Total	36 (41.4)	402.7	201.2	5	2,674	705.1	45.9										
Cumulative ^{e,f}		57.5	28.7	0.7	64.6	17	1.1										

NOTE: Data are no. (%) of participants, unless otherwise indicated. AMP, ampicillin; CAB, carbapenems; CAZ, ceftazidime; CIP, ciprofloxacin; CoNS, coagulase negative staphylococci; CPM, cefepime; GEN, gentamicin; GN, gram-negative; GP, gram-positive; ICU, intensive care unit; NAF, nafcillin; NT, not tested; PIP/T, piperacillin-tazobactam; TOB, tobramycin; VAN, vancomycin.

^a87 total BSI pathogens (overall BSI percentage includes 13.8% fungal, 9.1% anaerobic, and 2.3% other).

^bLIT = 100/(% drug resistance); 0 drug resistance represents an LIT of 100.

^cCumulative LIT: sum of LITs/no. of GN pathogens studied ($n = 11$).

^dBSI LIT: sum of LITs multiplied by percentage of frequency for each organism/cumulative percentage of GN pathogens ($n = 33.4\%$).

^eCumulative LIT: sum of LITs/no. of GP pathogens studied ($n = 7$).

^fBSI LIT: sum of LITs multiplied by percentage of frequency for each organism/cumulative percentage of GP pathogens ($n = 41.4\%$).