

Original Article



Factors influencing decision making and antibiotic prescribing patterns for the treatment of carbapenem-resistant *Enterobacteriaceae* (CRE) among non-infectious physicians in Thailand: a qualitative study

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ABSTRACT

The treatment of carbapenem-resistant *Enterobacteriaceae* (CRE) is diverse in each region due to the difference in local resistant patterns of CRE. We aimed to explore how physicians in Thailand decide on selection options for treating CRE infections. In this study, 25 physicians who were not infectious disease (ID) specialists participated in this semi-structured in-depth interview. We found that they, in general, did not provide empiric antibiotics for the treatment of CRE. However, some patients, e.g., those with prior carbapenems exposure may have brought CRE to physicians' attention. ID specialists played critical roles in both empiric and specific CRE treatment. There were multiple scenarios when CRE management deviated from recommendations, especially when physicians perceived that the evidence that supported the recommendations was weak. Several supportive factors, challenges, and improvements were also suggested. In conclusion, ID specialists, adequate information, and consistent implementation of infectious control policy are crucial to the treatment and prevention of CRE infection.

Keywords: Carbapenem-resistant *Enterobacteriaceae*; Decision Making; Inappropriate Prescribing; Qualitative Research

INTRODUCTION

Carbapenem-resistant *Enterobacteriaceae* (CRE) infection is associated with elevated mortality rates, which are higher than the odds in carbapenem-susceptible *Enterobacteriaceae* infected patients [1]. Currently, antibiotic options for CRE treatment are very limited. Polymyxin, fosfomycin, tigecycline, and aminoglycosides are the mainstay treatments [2-4]. In addition, several therapeutic strategies, e.g., using high-dose of antibiotics [3], double carbapenems

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[5], and combined antibiotics [4,5] are used to treat severe CRE infections to maximize treatment success. Although there are CRE treatment guidelines by the Infectious Diseases Society of America Guidance in 2020 [6], the resistance of CRE to antibiotics in each area is different due to the variety of common carbapenemase genes [3]. Therefore, the treatment of CRE infections was diverse locally. The superiority of the efficacy of each treatment option is not very well defined [7], and the treatment of CRE is highly dependent on the clinical experience of the physicians [8].

Because of the difficulty in treating CRE infection, inappropriate CRE treatment is common [9-11]. The prescription of inappropriate empirical treatment can lead to poor overall treatment outcomes [12] and high mortality [9]. Also, inappropriate specific antibiotic treatment, i.e., the delay of coverage antibiotics and the use of non-coverage antibiotics, is associated with poor clinical outcomes for CRE treatment [13]. The complexity of CRE treatment further depends on several other factors, e.g., physician knowledge, attitude, and perception of CRE [14,15], engagement of healthcare providers [16], and intervention efforts in medical decision-making [17]. Since appropriate antibiotic use is important for CRE treatment and physician decisions on how CRE infections are treated, empirically and specifically, are critical for the success in the management of CRE-infected patients. We aimed to find physicians' attitudes toward CRE infection situations and investigate how noninfectious disease (non-ID) physicians select antibiotic treatment patterns for CRE infection, to better understand factors influencing decision-making and antibiotic prescribing for CRE.

METHODS

Study setting and design

This qualitative study aimed to find non-ID physicians' attitudes toward CRE infection situations and investigated how they selected antibiotics for the treatment of CRE infection in an advanced-level government hospital in Chonburi, Thailand. Investigations with human subjects follow the ethical standards formulated in the Helsinki Declaration. The study was approved by the institutional review board of Chonburi Hospital (registration number ศบ.0032.102.9/209) and Burapha University (registration number Sci 077/2562). A semi-structured face-to-face interview was conducted from July 2020 to August 2020. The open-ended questions were developed by SS and discussed among the authors. The questions were then approved for content validity using the index of item objective congruence method by 3 ID medical specialists. All interviews were recorded, transcribed, and de-identified. All transcripts were re-checked and reviewed for accuracy and completeness for thematic analysis.

Population and samples

All physicians who had the authority to prescribe antibiotics and worked in an inpatient ward from July 2020 to August 2020 in the hospital were included. Because interviews required a minimum sample size of between 5 to 25 [18], the target enrollment according to this study was 25 attending physicians including attending staff, residents, and interns who were non-ID specialists. A purposive sampling strategy was used by inviting physicians via electronic mail to participate in a 30-minute confidential formal semi-structured interview, in which we asked for their opinions on antibiotic selection for CRE infection. The participants were asked to read and sign an informed consent form. During the interview, data were collected by audio recording and field notes.

Data and statistical analysis

The data were inspected and entered in Microsoft Excel and Microsoft Word, Windows version 10 (Microsoft, Washington, D.C., USA) for thematic analysis by SS. The data were categorized into meaningful units that represented the experiences and beliefs of participants. Coding and summarizing the results into themes related to physicians' attitudes, factors influencing decision-making, and antibiotic prescribing patterns for CRE among inpatient physicians were performed by SS and NL. The data were reported according to the Consolidated Criteria for Reporting Qualitative Research, an extension of Standards for Reporting Qualitative Research for interviews [19]. Discussion among the 4 authors for consensus was done when disagreement occurred. The transcript and the manuscript were not read by the participants after the study. Themes and illustrative quotes were translated from Thai to English by NL once when the manuscript was prepared.

RESULTS

Of the 36 residents or physicians-in-training invited, 25 (69%) participated (**Table 1**). The interviews revealed 13 themes related to factors influencing decision-making and antibiotic prescribing patterns for CRE (**Table 2**).

Theme 1. The importance of appropriate antibiotic use

The physicians recognized the importance of the appropriate use of antibiotics. The appropriate use of antibiotics led to better treatment efficacy and positive clinical outcomes in patients; shorter length of stay; lower mortality rate, occurrence, and spread of antibiotic resistance; and reduce cost of medical treatment.

Theme 2. Perceived negative impacts of CRE

The physicians agreed that CRE limited the treatment options, increased the mortality rate, aggravated the disease severity, inflated the cost of treatment, and was contagious. One of the physicians mentioned that "If we do not act better to manage the CRE now, we will not have any medicine for the treatment and the patients will die from CRE infection" (attending physician No. 5).

Theme 3. Patient characteristics that physicians perceived as risks for CRE infection

Most physicians agreed that it was nearly impossible to identify CRE-infected patients until a culture result was reported. Factors perceived as risks for CRE infection included a history of positive CRE culture, exposure to carbapenems, an outbreak of CRE in the current admitting

Table 1. Characteristics of 25 non-infectious physician participants

Characteristics	Intern	Resident	Total
Age (yr)		27.80 ± 1.76	
Sex			
Male		14 (56)	
Female		11 (44)	
Specialties			
Medicine	7	2	9 (36)
Surgery	5	2	7 (28)
Pediatric	3	2	5 (20)
Orthopedic	3	1	4 (16)

Values are presented as mean ± standard deviation or number of participants (%).

Table 2. Themes and illustrative quotations identified from semi-structured interviews with 25 inpatients physicians

Topic	Theme	Illustrative quotation
1. The importance of appropriate antibiotic use	Improved treatment efficacy or response to the treatment	(1) "If (the antibiotic use) is appropriate, patients are going to respond well to the treatment. This is good for the patients." (No. 13_ped-it-2) (2) "Basically, patients are not treated if we give medications inappropriately." (No. 18_ort-it-3) (3) "Inappropriate drugs lead to unresponsive to the treatment." (No. 20_ort-rd-3) (4) "We can treat the patients when (antibiotic) drugs match the bacteria." (No. 24_sur-rd-3)
	Reduced hospitalization period	(5) "(With appropriate antibiotic use), there is no complication and hospital days are reduced." (No. 13_ped-it-2)
	Reduced mortality rate	(6) "(Patients) would survive the infection if drug use is appropriate. This would reduce the induction of antibiotic resistance in the future." (No. 10_med-it-1) (7) "I think it might reduce the death rate." (No. 15_ped-it-3)
	Reduced spreading of antibiotic-resistant bacteria	(8) "(It) can reduce the resistant bacteria in the hospital." (No. 8_sur-it-3) (9) "If (antibiotic) drugs are used correctly in the first place, patients will have lesser exposure to the drug. This would reduce the chance for multidrug resistance and new case (of patients infected with) resistant bacteria." (No. 14_ped-it-1) (10) "Basically, patients are not treated if we give medications inappropriately. This might increase the contamination and induce further spreading of resistant organisms." (No. 18_ort-it-3) (11) "Inappropriate drugs increase the risk for drug resistance which increase the rate of drug-resistant organisms." (No. 20_ort-rd-3) (12) "Eradicating bacteria in the patients controls the spreading of the microorganisms." (No. 22_ped-rd-2) (13) "Even a patient that we treat affects the rate of antibiotic resistance in the hospital. If (the antibiotics are provided) appropriately, this will prevent further development of antibiotic-resistant organisms." (No. 24_sur-rd-3)
	Reduced hospitalization cost	(14) "Patients would have lesser exposure to antibiotics if our patients are treated appropriately. I think it affects drug use at the hospital level." (No. 14_ped-it-1) (15) "Inappropriate drug selection increases the rate of drug-resistant organisms. The hospital would pay a higher cost." (No. 20_ort-rd-3)
2. Perceived negative impacts of CRE	Limited treatment options	(16) "There is no drug to be used. We have fewer options." (No. 2_med-it-2) (17) "There are not many antibiotics for the treatment of bacteria that resist carbapenems if (patients are) infected by these organisms. This is dangerous to the patients." (No. 6_sur-it-3) (18) "We have decreased number of antibiotics and the disease progresses while we do not have antibiotics." (No. 13_ped-it-2)
	Increased mortality rate	(19) "We (will) have problems in choosing antibiotics in the future." (No. 19_med-rd-3) (20) "(CRE) are resistant bacteria, are aggressive, and have higher mortality rate." (No. 3_med-it-3) (21) "The chance of death is higher than normal." (No. 11_med-it-2) (22) "(We) have fewer drugs (for CRE which) have high mortality rate and complications from antibiotics." (No. 4_med-it-1) (23) "(CRE) must be controlled because they are the cause of death in a lot of patients at the medical ward that I am in charge of." (No. 5_med-it-3)
	Increased disease severity	(24) "(CRE are) resistant bacteria that make patients sicker." (No. 8_sur-it-3) (25) "(CRE) worsen patient condition." (No. 24_sur-rd-3) (26) "(CRE) infection is serious. There were patients with this infection. They did not respond to antibiotics. They were getting worse." (No. 12_sur-it-1)
	Increased treatment cost	(27) "(CRE) render an increase in antibiotic use for the treatment." (No. 8_sur-it-3) (28) "For antibiotic-resistant bacteria, board spectrum antibiotic must be used." (No. 14_ped-it-1) (29) "The important issue is the treatment cost, and the use of antibiotics for empirical treatment that is coverage." (No. 20_ort-rd-3)
	Contagiousness	(30) "If the culture result shows CRE, the vigilance for spreading is required." (No. 22_ped-rd-2) (31) "If it happens frequently, there is a chance for contamination and transmission to other patients." (No. 11_med-it-2) (32) "Even if it can be cured but the chance of spreading is there." (No. 25_sur-rd-3) (33) "In the view of epidemiology, the number of CRE infected patients has been increasing. Now, if the patients' symptoms are getting worse from nosocomial infection, we have to consider drugs that cover CRE while back then we think of <i>Acinetobacter baumannii</i> or ESB." (No. 5_med-it-3)
3. Patient characteristics that physicians perceived as risks for CRE infection	History of positive CRE culture	(34) "When the previous culture result was positive for CRE and the current clinical is worsening, I would consider CRE as the cause of infection." (No. 2_med-it-2) (35) "(I would think of CRE if the patient) was infected by CRE within 3 months." (No. 3_med-it-3) (36) "(I would think of CRE in) patients with the history of hospitalization or have CRE positive result within 60–90 days." (No. 8_sur-it-3) (37) "The patient was infected with CRE before. That makes me think of CRE this time." (No. 11_med-it-2) (38) "I really think of CRE infection when the patient has a history of CRE infection that carries on to this current admission." (No. 18_ort-it-3)
	History of carbapenems usage	(39) "(The patient) was treated by carbapenem frequently or within 3 months." (No. 3_med-it-3) (40) "(I would think of CRE if the patient) was treated by carbapenems before." (No. 17_ort-it-3)

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Table 2. (Continued) Themes and illustrative quotations identified from semi-structured interviews with 25 inpatients physicians

Topic	Theme	Illustrative quotation	
	History of or current outbreak of CRE in the ward	(41) “(I would think of CRE in patients) that have already been treated with carbapenem and infection develops after that; has a history of CRE infection; and was infected with ESBL and treated by carbapenem within 3 months.” (No. 19_med-rd-3)	
		(42) “(I would think of CRE infection) when there is CRE outbreak or the nearby bed has CRE infection.” (No. 15_ped-it-3)	
		(43) “If there is CRE outbreak at the time, I would empirically treat patients with antibiotics that cover CRE.” (No. 22_ped-rd-2)	
		(44) “(I would think of CRE in patients) that received board spectrum antibiotics before and was in a ward with CRE contamination.” (No. 14_ped-it-1)	
	History of hospitalization or frequent history of hospital usage	(45) “(I would think of CRE in patients who are) not responding to antibiotics with the history of staying in an area with CRE outbreak.” (No. 23_ped-rd-2)	
		(46) “Patients that come to the hospital frequently.” (No. 3_med-it-3)	
		(47) “(I would think of CRE in) patients that already at risk, for example, enter the hospital frequently or treated with antibiotics before. Also, in patients with weak immunity.” (No. 9_surg-it-2)	
	Prolonged hospitalization	(48) “(Patients) with the history of an inpatient admission within one month.” (No. 17_ort-it-3)	
		(49) “(CRE are) mostly found in cases with prolonged hospitalization, e.g., children who stay in the hospital for a long time and develop a fever.” (No. 22_ped-rd-2)	
		(50) “In cases that were treated with long-duration antibiotics or admitted for longer than 14 days.” (No. 15_ped-it-3)	
		(51) “In patients who are admitted for a while and then suddenly have a new onset of fever with rapid worsening of symptoms.” (No. 24_sur-rd-3)	
	Immunocompromisation	(52) “The patient staying at the hospital for a long time easily makes me think of CRE because I do not think of CRE in newly admitted patients.” (No. 25-sur-rd-3)	
		(53) “(I would think of CRE in a patient who) has a history of CRE infection and is an immunocompromised host.” (No. 17_ort-it-3)	
		(54) “(I would think of CRE in) patients that are already at risk, for example, enter the hospital frequently or treated with antibiotics before. Also, in patients with weak immunity.” (No. 9_surg-it-2)	
	Septicemia or febrile neutropenia	(55) “patients with very high-risk or febrile neutropenia” (No. 1_med-it-3)	
		(56) “In patients with signs and symptoms of clinical septic, I would think that the causative organisms must be more virulence (than usual).” (No. 8_sur-it-3)	
Intubation	(57) “In patients with endotracheal tube intubation, when they are collected for samples for bacterial culture, most of the results are CRE positive.” (No. 10_med-it-1)		
Neonates	(58) “During the time of CRE outbreak, I would provide empirical treatment for CRE, especially in neonates.” (No. 22_ped-rd-2)		
No improvement after empirical treatment with carbapenem	(59) “In patients who are being treated with meropenem and are still positive for gram-negative bacilli” (No. 1_med-it-3)		
	(60) “(I would think of CRE in patients) who are being empirically treated with a carbapenem and shows no improvement.” (No. 3_med-it-3)		
	(61) “(I would think of CRE) in patients who have been given antibiotics but shows no improvement. Patients who are still getting worse.” (No. 11_med-it-2)		
	(62) “In the case that children are hospitalized for a long time but just have a fever that does not respond to meropenem” (No. 22_ped-rd-2)		
4. Antibiotic-resistant bacteria, other than CRE, that physicians considered when the culture result was still pending	ESBL	(63) “In patients already treated with meropenem but clinical symptoms are not improving” (No. 21_med-rd-3)	
		(64) “(I usually do not think of CRE empirical treatment. For CRE, I usually wait for culture results. At most, I think of ESBL.” (No. 18_ort-it-3)	
		(65) “For empirical treatment, mostly I think of ESBL.” (No. 21_med-rd-3)	
		(66) “If (the gram staining) shows gram-negative bacteria and I suspect antibiotic-resistant bacteria, I would think of <i>A. baumannii</i> before CRE.” (No. 1_med-it-3)	
5. Characteristics of CRE positive patients that physicians postponed the antibiotics	<i>A. baumannii</i>	(67) “Earlier at the hospital, we usually find <i>A. baum(anii)</i> more frequently than CRE. If patients have been treated with carbapenem but develop a new onset fever, I would give empirical treatment that covers <i>A. baum(anii)</i> .” (No. 2_med-it-2)	
	Mild severity	(68) “Patients do not have a severe infection or patients with culture samples are from a local source, e.g., drainable abscess.” (No. 6_sur-it-3)	
		Improved clinical symptoms	(69) “I had found patients with hemoculture positive for CRE but they responded to ceftriaxone. The fever was gone. They could pee or eat. I would not give them antibiotics. I would reconsider antibiotics if later their symptoms worsen.” (No. 2_med-it-2)
			(70) “In patients who stay at the hospital for a long time and have already treated for sepsis and do not have pneumonia as shown by X-ray. Also, in patients whose sputum from tracheal suction is positive for CRE but have good clinical symptoms (e.g., no fever, no hypotension), i.e., the culture result does not correlate with clinical symptoms” (No. 5_med-it-3)
	Palliative or supportive care	(71) “In palliative care in newborn, which can be found from time to time” (No. 13_ped-it-2)	
		(72) “NR (do not resuscitate)” (No. 9_surg-it-2)	
		(73) “supportive care case” (No. 19_med-rd-3)	

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Table 2. (Continued) Themes and illustrative quotations identified from semi-structured interviews with 25 inpatients physicians

Topic	Theme	Illustrative quotation
	Colonization or contamination	<p>(74) “(I postpone antibiotics when) I suspect the colonization. When patients show no clinical sign at all. No fever. No cough. No sputum.” (No. 3_med-it-3) (No. 14_ped-it-1)</p> <p>(75) “(I postpone antibiotics when) I think this is not an infection but colonization. I would consider clinical symptoms including fever, blood pressure, and infiltration on X-ray film.” (No. 4_med-it-1)</p> <p>(76) “(I postpone antibiotics when) I suspect contamination or colonization. I once found a case that CRE were found in the urine but clinical symptoms in patients improved even when the board spectrum antibiotics have not given. When the urine culture was reordered, the result was negative (for CRE). Or in the case that tracheal suction is positive for CRE but chest X-ray is normal.” (No. 15_ped-it-3)</p> <p>(77) “(I postpone antibiotics) in case that patients' clinical signs and symptoms are stable (e.g., no fever) or improving, which does not correlate with the culture result. It might be bacterial colonization or contamination.” (No. 24_sur-rd-3)</p>
6. Approaches for the empiric treatment of CRE	No empirical treatment	<p>(78) “I have never empirically treated for CRE. I always wait for the culture result.” (No. 23_ped-rd-2)</p> <p>(79) “If the infection is really caused by CRE, I do not know how to empirically treat. I have to wait for the culture and sensitivity result.” (No. 25_sur-rd-3)</p>
	Empirical treatment with carbapenem	<p>(80) “Normally I do not think of CRE. I wait for the culture result.” (No. 17_ort-it-3)</p> <p>(81) “Do not empiric for CRE.” (No. 20_ort-rd-3)</p> <p>(82) “Mostly, I would empirically treat with meropenem. I would step up the treatment when I have the culture result.” (No. 10_med-it-1)</p>
	Empirical treatment with colistin and fosfomycin	<p>(83) “Surgeons do not order these medicines. Even when we suspect CRE, we would order carbapenem and wait for ID specialists recommendation.” (No. 8_sur-it-3)</p> <p>(84) “I would treat empirically as a general infection by starting meropenem. Even I suspect CRE, I would not stop the previous antibiotics but add more drugs if the symptoms are not better.” (No. 24_sur-rd-3)</p> <p>(85) “For other gram-negative, e.g., <i>Escherichia coli</i> or <i>Klebsiella pneumoniae</i>, I would use colistin with fosfo(mycin)” (No. 1_med-it-3)</p> <p>(86) “I would empirically treat by considering the previous culture and sensitivity results. The drugs that are still effective are usually colistin with fosfomycin” (No. 3_med-it-3)</p> <p>(87) “Fosfomycin with colistin as the main treatment” (No. 5_med-it-3)</p> <p>(88) “Colistin combined with fosfomycin” (No. 11_med-it-2)</p> <p>(89) “I would consider the gram stain result. If the result is possibly CRE, I would consider colistin with fosfomycin. But this might be changed in the future since resistance to colistin with fosfomycin has become more common.” (No. 19_med-rd-3)</p>
	Empirical treatment with colistin based combination	<p>(90) “I would consider sensitivity results in other patients in the same ward, to see that which drugs are still effective to CRE. In some periods, bacteria are still sensitive to colistin. I might add other antibiotics too.” (No. 4_med-it-1)</p> <p>(91) “I would add colistin when I think it is CRE.” (No. 14_ped-it-1)</p>
	Empirical treatment with aminoglycosides based combination	<p>(92) “In case of UTI, I might consider fosfomycin with Amikin®. If it is caused by <i>E. coli</i>.” (No. 21_med-rd-3)</p> <p>(93) “Normally I would use drug combinations, depending on which that has been used in the patient. Aminoglycosides are probably always the must. If the patient is already being treated with broad-spectrum antibiotics, I would consider fosfomycin.” (No. 15_ped-it-3)</p>
	Empirical treatment based on site of infection	<p>(94) “(I would) see if the drug can penetrate the source of infection.” (No. 3_med-it-3)</p> <p>(95) “It is necessary to use rather broad-spectrum antibiotics for the empirical treatment of CRE, depending on the source of infection and organisms. For example, for UTI caused by <i>E. coli</i>, I would consider fosfomycin with Amikin®.” (No. 21_med-rd-3)</p>
	Empirical treatment based on previous culture results	<p>(96) “If the patient has a history of bacterial resistance or CRE infection, I would look at the previous culture and sensitivity result.” (No. 6_sur-it-3)</p>
	As ID specialist recommendation	<p>(97) “I do not know what (antibiotics) to use. I will wait for ID.” (No. 8_sur-it-3)</p> <p>(98) “If meropenem is administered but the patient is not better, I would suspect CRE. All the suspected CRE cases are consulted with the ID specialists” (No. 22_ped-rd-2)</p> <p>(99) “If I must treat CRE infection, I would wait for the culture and sensitivity result and then consult ID.” (No. 24_sur-rd-3)</p>
7. References for the approaches for empiric treatment of CRE	International guideline	<p>(100) “Mainly, I use the Sanford Guide to Antimicrobial Therapy.” (No. 16_ort-it-3)</p> <p>(101) “CDC” (No. 20_ort-rd-3)</p>
	Thai guideline	<p>(102) “(I) follow the (guideline from) the Infectious Disease Association of Thailand” (No. 15_ped-it-3)</p>
	Local guideline	<p>(103) “(I follow) the empirical strategy that I learned from where I graduated (Faculty of Medicine Siriraj Hospital).” (No. 4_med-it-1)</p> <p>(104) “The recommendation by Chonburi Hospital that is behind the DUE form.” (No. 25_sur-rd-3)</p>
	Conference	<p>(105) “Mainly from the infectious academic short courses.” (No. 21_med-rd-3)</p> <p>(106) “From conferences.” (No. 5_med-it-3)</p>
	Research article	<p>(107) “From researches conducted in Thailand.” (No. 5_med-it-3)</p>
	Training	<p>(108) “It is the experience that I got from ID ward. There is no specific guideline. It depends on which drugs that the bacteria are still sensitive to.” (No. 19_med-rd-3)</p>
	Learning and experience	<p>(109) “I evaluate the empirical treatment for CRE using my experience obtained from working in inpatient wards.” (No. 4_med-it-1)</p>

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Table 2. (Continued) Themes and illustrative quotations identified from semi-structured interviews with 25 inpatients physicians

Topic	Theme	Illustrative quotation
8. Approaches for the specific treatment of CRE	ID specialist recommendation	(109) "(I do) not (have a) specific (reference). Several of the references are similar so I use those references and my own experiences. I do not have the main specific source of information." (No. 3_med-it-3)
		(110) "I have never read guidelines. I follow what the teachers taught me." (No. 15_ped-it-3)
		(111) "From what ID teachers taught" (No. 21_med-rd-3) (No. 22_ped-rd-2)
		(112) "No reference. I use what I have learned, experience, and I consult my ID teacher for all of the CRE patients." (No. 23_ped-rd-2)
		(113) "From my experiences" (No. 24_sur-rd-3)
		(114) "I know nothing (about the empirical treatment). I adjust the treatment according to culture and sensitivity results and consult ID specialists." (No. 9_surg-it-2)
	Specific treatment based on susceptibility test	(115) "I follow the suggestions from ID." (No. 25-sur-rd-3)
		(116) "I order antibiotics according to culture results and mainly consult ID specialists. If I think this can wait, I wait for the results." (No. 18_ort-it-3)
		(117) "I would consider culture result. Antibiotics are adjusted according to the sensitivity result." (No. 11_med-it-2) (No. 12_sur-it-1) (No. 18_ort-it-3) (No. 20_ort-rd-3) (No. 22_ped-rd-2) (No. 24_sur-rd-3)
	Specific treatment based on MIC	(118) "I would choose an antibiotic with the narrowest spectrum that the bacteria are still sensitive to." (No. 23_ped-rd-2)
		(119) "In case of urgency, I would give antibiotics according to the sensitivity result and then consult ID specialists in almost all cases." (No. 9_surg-it-2)
	Specific treatment based on patient clinical symptoms	(120) "I would consider culture results and consult ID specialists for adjusting antibiotics." (No. 10_med-it-1)
		(121) "I normally consider the MIC of antibiotics for each organism. Some drugs such as fosfomycin do not have MIC data reported. I would order other antibiotics and call the (microbiological) lab for the data." (No. 15_ped-it-3)
	Combination treatment	(122) "(I would) see whether the kid who is using antibiotics responds to the drug or not. Sometime <i>in vitro</i> and <i>in vivo</i> results do not agree." (No. 14_ped-it-1)
		(123) "I chose antibiotics based on drug sensitivity. The regimen should have at least one drug that the bacteria are sensitive to. Mostly I would consider colistin with fosfomycin, colistin with a sensitive drug, or a sensitive aminoglycoside. If the bacteria are sensitive to both antibiotics in the regimen, that is great." (No. 1_med-it-3) (No. 5_med-it-3)
9. Reasons for prescribing practices that deviate from CRE treatment guidelines	Specific treatment based on site of infection	(124) "When CRE are possible, I would normally choose colistin for the 2 drugs regimen. The other might be fosfomycin." (No. 3_med-it-3)
		(125) "I give 2 drugs that the bacteria are sensitive to, according to the sensitivity result, to increase the cure rate and reduce the chance for resistance." (No. 19_med-rd-3)
		(126) "I prefer drug combination to one drug. I do not have any antibiotics in mind. I always consult ID specialists." (No. 13_ped-it-2)
	Dose adjustment	(127) "(Drug selection should) agree with the source of infection and sensitivity result. The duration should be as short as possible. If the source is blood I would order antibiotics for 14 days but if the source is the other, the duration is the shortest and as necessary." (No. 19_med-rd-3)
		(128) "The duration of the treatment depends on the source of infection." (No. 2_med-it-2)
		(129) "(I would) chose based on the infected organ. If the antibiotic reaches the target organ. Also, base on the route of administration." (No. 6_sur-it-3)
	Specific treatment based on ID specialist recommendation	(130) "The dose on the first day is the full dose. The doses for the following days are adjusted according to the renal function." (No. 2_med-it-2)
		(131) "If the cause of infection is antibiotic-resistant bacteria, I would order antibiotics that are recommended by the ID specialist." (No. 7_sur-it-1) (No. 8_sur-it-3)
		(132) "I prefer drug combination to one drug. I do not have any antibiotics in mind. I always consult ID specialists." (No. 13_ped-it-2)
	History of drug allergy	(133) "Mostly I consult ID specialists for every patient with CRE infection. This is especially with the drugs that I am not used to, I always ask the ID specialist before I order the drugs." (No. 25-sur-rd-3)
		(134) "Even the culture result is there, I do not adjust the antibiotics. I wait for suggestions from ID specialists." (No. 17_ort-it-3)
		(135) "Mostly I consult ID specialists for the drug adjustment." (No. 24_sur-rd-3)
	Cited studies were small	(136) "I always comply with the guidelines except for when the patient has drug allergy." (No. 6_sur-it-3)
		(137) "Some articles are from very small studies." (No. 21_med-rd-3)
10. Positive reinforcements for the management of CRE infection	Sufficient ID specialists	(138) "Reinforcement? I think enough ID specialists for consultation is helpful." (No. 8_sur-it-3)
		(139) "Sufficient number of ID specialists. This allows the response to be in time." (No. 12_sur-it-1)
		(140) "ID specialists who provide the suggestion in time" (No. 13_ped-it-2)
		(141) "When the ID specialist is consulted, the recommendation is usually suggested in time within 24 hours." (No. 17_ort-it-3)
		(142) "ID specialists who are accessible and provide useful suggestions in time." (No. 20_ort-rd-3)

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Table 2. (Continued) Themes and illustrative quotations identified from semi-structured interviews with 25 inpatients physicians

Topic	Theme	Illustrative quotation
11. Obstacles for the treatment of CRE infection	Infection Control	(143) "The hospital set goals to control the infection; implements patient isolation policy; and provides protective dressing." (No. 8_sur-it-3)
	DUE policy and process	(144) "DUE policy and the process related with the policy can help. For example, if the current antibiotics are not matched with the culture result, ID specialists can cancel the current antibiotics. This kind of system limits the use of antibiotics." (No. 10_med-it-1)
		(145) "I agree with setting up systems. I also agree with the antibiotic drug list that limits access to antibiotics according to the specialties. Reminders and aids such as drug dosing summary. All are helpful." (No. 21_med-rd-3)
		(146) "The DUE form has the antibiotic dose summary which is very helpful. We (, physicians,) use the summary in adjusting doses in patients." (No. 24_sur-rd-3)
	Difficulty in the treatment of CRE	(147) "(CRE are) antibiotic-resistant bacteria. They are hard to treat. Difficult to eradicate." (No. 7_sur-it-1)
		(148) "(CRE are) antibiotic-resistant bacteria. Taking care (of the infected patients) is difficult and must be done carefully." (No. 9_surg-it-2)
		(149) "(CRE are) antibiotic-resistant bacteria that is very difficult to treat when contracted. The cure rate is low. Leaving the hospital is not easy. A lot of complications. They are hard to treat." (No. 17_ort-it-3)
		(150) "(CRE are) antibiotic-resistant bacteria that are difficult to treat and have very few drugs for the treatment." (No. 23_ped-rd-2)
	Lack of confidence or knowledge	(151) "I am afraid of antibiotic regimen adjustment. I have to consult ID specialists." (No. 2_med-it-2)
		(152) "I do not know the guideline for selecting antibiotics for the treatment of CRE." (No. 7_sur-it-1)
		(153) "I do not know what antibiotics should be used." (No. 8_sur-it-3)
12. Obstacles for the control of CRE infection	Lack of or inaccessible to necessary data	(154) "I do not know how often the antibiogram is updated. It is not accessible." (No. 3_med-it-3)
		(155) "I have never accessed the official antibiogram." (No. 4_med-it-1)
		(156) "Mainly, I have never seen the antibiogram. I do not know where it is and have never seen anybody look at or access to it." (No. 6_sur-it-3)
		(157) "MIC of antibiotics in the hospital, and outbreak data, we mostly know them by ourselves or word-of-mouth. There is no source of information. If we know the information, this should affect how we chose antibiotics." (No. 15_ped-it-3)
		(158) "The outbreak data. If we know the data, we would choose antibiotics better." (No. 19_med-rd-3)
		(159) "The outbreak data affect (how we chose antibiotics) but we usually do not know." (No. 25_sur-rd-3)
		(160) "The most important information that I think of is antibiogram. Every time that antibiotic use is evaluated, ID specialists would give information via case conference but we rarely talk about antibiograms in the hospital. Do not know the information. Do not know how to access the antibiogram." (No. 21_med-rd-3)
	Insufficient ID specialists	(161) "I think there are not enough ID specialists. But now, in newborn cases, I would consult newborn specialists but if the case is more complicated, I would consult ID specialists." (No. 22_ped-rd-2)
		(162) "The number of ID specialists is, in fact, barely sufficient. But I understand that there are a few ID specialists. Few medical students chose this specialty." (No. 21_med-rd-3)
	"Not my problem" attitude	(163) "(CRE are) important because they resist antibiotics. But in the viewpoint of me as an orthopedic residence, CRE might not be related to me since I rarely come across with CRE." (No. 16_ort-it-3)
		(164) "I am not sure about the other ward but in orthopedic ward, I barely encounter CRE cases. Mostly I find ESBL that resist carbapenems." (No. 18_ort-it-3)
		(165) "In surgery, I usually do not come across with CRE. Maybe 1–2 cases per month. Usually in chronic cases that have prolonged hospitalization." (No. 25_sur-rd-3)
		(166) "I found CRE from time to time. I think the incidence is the same but maybe because I am a surgeon so I do not usually see it." (No. 12_sur-it-1)
	Variation in the strictness in the infection control implementation	(167) "Previously, when we faced CRE infected patients, we seriously isolated the patients. But nowadays, as we can see, there are a lot of patients. We can barely isolate the patients. We just have the sign for the isolation." (No. 2_med-it-2)
		(168) "Not a lot of people do anything. I think there should be training. I see that the infectious control committee tries to initiate something. But people who work with patients usually do not pay attention (to the control process). The hospital can force some wards to participate. In some wards, infectious control is fully implemented but in some wards, there is no implementation at all. I do not have to wear or do anything. The standard is not the same." (No. 15_ped-it-3)
	Normalization of CRE	(169) "I see CRE infection normally. Spreading from patients to patients or health care professionals is the carrier. Sometimes there are no cases but sometimes there are 2–3 cases per week." (No. 9_surg-it-2)
		(170) "CRE are antibiotic-resistant bacteria. They are generally important just like the antibiotic-resistant organisms." (No. 15_ped-it-3)
		(171) "Now there are a lot of serious (CRE) situations in the hospital. Mostly, patients in our hospital already receive antibiotics a lot. Some of the patients already receive CRE empirical treatment from lower-level hospitals (before the patients are sent to us)." (No. 21_med-rd-3)
13. Suggestions for the management of the CRE situation	Accessible necessary information	(172) "Antibiogram should be available in every ward, maybe in a colorful hard paper so it attracts our attention." (No. 3_med-it-3)
		(173) "The accessible antibiogram should be sent via Line groups of residents or ID specialists or head of residents." (No. 4_med-it-1)

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Table 2. (Continued) Themes and illustrative quotations identified from semi-structured interviews with 25 inpatients physicians

Topic	Theme	Illustrative quotation
		(174) "Print the data or QR code for the data. Put the print at wards or important documents on the wards." (No. 6_sur-it-3)
		(175) "Antibiogram should be at the nurse station so we can use the antibiogram with the DUE form." (No. 24_sur-rd-3)
		(176) "I think the data of the outbreak are important but physicians usually do not know. Medical department should be informed so the data can be disseminated to doctors." (No. 25_sur-rd-3)
		(178) "There should be the channel for physicians to access necessary related information. The information should be at the ward, not in the medical lounge because physicians usually do not use the lounge." (No. 21_med-rd-3)
	Rapid reporting of culture result	(179) "I want Lab Alert for CRE, just like the alert for lab results for critical care. I know the notification is available for the nurses but it does not direct to physicians. If the notification is direct to us, we can adjust medications for the patient earlier, especially for patients with sepsis." (No. 2_med-it-2) (No. 5_med-it-3)
		(180) "There is no notification when the type of organisms is confirmed. Sometimes, I waited for 1–2 days. I want notifications or alerts for all antimicrobial resistance, not only CRE. Physicians should be called, just like the other lab alert." (No. 7_sur-it-1)
		(181) "I want that physicians are notified when the result for specific culture is available. There was a case when a physician does not know or knows later (that his/her patient is infected with CRE) and the patient is isolated in haste. In some cases, the patient is not isolated in time." (No. 23_ped-rd-2)
	Strict implementation of infection control practice	(182) "Really, CRE is somewhat not common. If we all collaborate seriously, the outbreak is prevented. For example, standard operating procedures are available and clear, contact precaution strictly complies." (No. 7_sur-it-1)
		(183) "The patient should be separated. Into separated area or ward. Inanimate objects should also be personalized and not pooled with other patients." (No. 10_med-it-1)
		(184) "Everyone should know, think, and practice in the same way. Practice the same standard. All the signs and warnings should be consistent." (No. 15_ped-it-3)
		(185) "A meeting should be arranged to standardize the (infectious control) practice." (No. 24_sur-rd-3)
	Management of the facility	(186) "In case that a patient infected with antibiotic-resistant bacteria are found, that patient should be admitted in a separate ward. Nowadays, this type of patient is admitted and stays with other patients. They are placed into infectious wards beyond the capacity of the wards." (No. 4_med-it-1)

CDC, Centers for Disease Control and Prevention; CRE, carbapenems-resistant *Enterobacteriaceae*; DUE, drug use evaluation; ESBL, extended-spectrum beta-lactamase; ID, infectious disease; IT, intern; MED, medicine; PED, pediatric; SUR, surgery; RD, residency; UTI, urinary tract infection; MIC, Minimal Inhibitory Concentration.

ward, frequent hospital admission, or frequent antibiotic exposure while being admitted, and long hospitalization. Besides, cues for CRE infection included being immunocompromised, having septicemia or febrile neutropenia, being intubated, being a newborn, and not responding to a carbapenem empirical treatment.

Theme 4. Antibiotic-resistant bacteria, other than CRE, that physicians considered when the culture result was still pending

In a case where patients treated empirically with a carbapenem deteriorated while the culture results were pending, physicians may have considered other gram-negative bacteria, e.g., *Enterobacteriaceae* with Extended-Spectrum Beta-Lactamases and *Acinetobacter baumannii*, as the causative organism before considering CRE.

Theme 5. Characteristics of CRE-positive patients that physicians postponed the prescription of antibiotics

The physicians did not prescribe antibiotics for CRE empiric treatment, even though later the culture result was CRE positive, when they encountered patients with mild severity or improved clinical symptoms, e.g., no fever, or able to have food by mouth; patients who were on palliative or supportive care or on "do not resuscitate" status; or when the physicians evaluated that the positive results derived from bacterial colonization or contamination.

Theme 6. Approaches for the empiric treatment of CRE

Most physicians did not think of CRE as a causative organism until the culture result was reported. However, when the empiric was essential, regimens often recommended by experienced ID specialists included carbapenem, colistin plus fosfomycin, colistin-based, and aminoglycoside-based combinations (Table 3). Factors that affected the selection of

Table 3. Empirical treatment regimens for CRE infections

Regimens of empiric treatment	Physician	Unit (ward) in the hospital
Colistin + Fosfomycin	6 (24)	Medicine 6
Colistin based combination	2 (8)	Medicine 1, Pediatric 1
Aminoglycoside based combination + Fosfomycin (for urinary tract infection)	2 (8)	Medicine 1, Pediatric 1
Antibiotics that CRE were susceptible to from previous cultures	1 (4)	Surgery

Values are presented as number (%).

CRE, carbapenem-resistant *Enterobacteriaceae*.

antibiotics included the site of infection and the history of antibiotics used for the treatment of the previous CRE infection. Some physicians always wait for recommendations from ID specialists.

Theme 7. References for the approaches for empiric treatment of CRE

References for the approaches for empiric treatment of CRE used by the physicians included the guideline from The United States Centers for Disease Control and Prevention (CDC), The Sanford Guide to Antimicrobial Therapy, the guideline from the Infectious Disease Association of Thailand, and local guidelines. In addition, the physicians used information from ID conferences, articles published in Thai medical journals, knowledge and experiences obtained during the training, and recommendation by ID specialists to assist in the selection of the empirical treatments.

Theme 8. Approaches for the specific treatment of CRE

Physicians selected antibiotics for the specific treatment based on culture and resistant testing results, the Minimal Inhibitory Concentration (MIC) of antibiotics, and the clinical symptoms of the patients during the treatment. The site of infection and dose recommendation also affected the selection of the drug regimen. In addition, some physicians whose specialty was not internal medicine always consulted ID specialists.

Theme 9. Reasons for prescribing practices that deviate from CRE treatment guidelines

The deviation from guidelines also occurred when patients had a history of drug allergy or when the physicians perceived that the strength of the recommendation was weak.

Theme 10. Positive reinforcements for the management of CRE infection

Positive reinforcements for the management of CRE infection included enough ID specialists in the hospital, systems for CRE Infection Control and Prevention (ICP), and drug use evaluation (DUE) policies and processes.

Theme 11. Obstacles to the treatment of CRE infection

Obstacles to the treatment of CRE infections included the kidney toxicities from medications, the lack of confidence and in-depth knowledge for the treatment of CRE infection, and the unavailability of or inaccessibility to necessary information including local CRE situations and treatment guidelines.

Theme 12. Obstacles to the control of CRE infection

The control of CRE infection in the hospital was impeded by the insufficient number of ID specialists, the perception that CRE did not impact their wards or units, the relaxed enforcement of infection and control policy and measures in the hospital, and the perception that CRE occurred sporadically and was not troublesome.

Theme 13. Suggestions for the management of the CRE situation

Relevant information should have been available and accessed easily. The final culture reports should have been directly notified to the physicians, especially in sepsis or septicemia patients. The ICP processes should have been standardized and used similarly in every unit in the hospital. The optimum patient distancing and the separation of CRE-infected patients should have been fully implemented.

DISCUSSION

In this study, participating physicians believed that appropriate antibiotic use was important for the treatment of CRE patients, agreeing with the study by Zilberberg et al. [13]. Also, physicians agreed that selecting antibiotics for the treatment of CRE infection was difficult because of multiple antimicrobial use and limited options, agreeing with other studies [2,7]. Several factors that were also reported by Weston et al. [20] and the CDC [21] were used to estimate the likelihood of CRE infection, including a history of positive CRE culture, intubation, long hospitalization, exposure to carbapenems, patient transferred from an area known to have CRE outbreaks, frequent admission to the hospital or frequent exposure to antibiotics. We also found that recommendations from ID specialists heavily influenced the selection of empirical CRE treatment by physicians. Specific treatments found in this study agreed with Daikos et al. [22] and included combination therapies that had colistin as a core with fosfomycin and aminoglycoside as supplements or the use of at least 2 drugs that the bacteria were susceptible to. However, while Daikos et al. [22] found the use of double carbapenem therapy in their study, it was not reported in ours. This might be because using double carbapenem is not practical when the MIC is more than 8 mg/L [23].

The selection of empirical therapy for CRE Infection was influenced by the specialty of the physicians. Most internal medicine physicians were able to prescribe consistently with the antimicrobial treatment guidelines [6,24,25]. On the contrary, surgeons, and orthopedists reported that they usually waited for recommendations from ID specialists. The physician attributes such as their specialty, clinical experience, and practice decisions may have influenced the physicians' decision-making regarding CRE infection. This issue is consistent with other studies [8,26]. Other factors involved in the selection of antibiotics for specific treatments that were also reported in the literature were the culture reports, site of infection, MIC, pharmacokinetics and pharmacodynamics, disease condition, and clinical manifestations of the patient [7,23]. In addition, antibiogram and antibiotic control policies in the hospitals may have influenced the determination of a prescribing pattern, agreeing with the current operational guidelines of Thailand [27].

The limitation of this research is that the interviews did not include all types of specialists available in the hospital. We believe that this problem did not affect the quality of this study because the inpatient care system operating in this hospital has non-ID specialists as the primary medical care providers. ID specialists with fellowships usually provide supervision for the residents or care for more critical patients. Next, the first author is a registered pharmacist and member of the committee for antimicrobial-resistant management both at the hospital level and health district level. Therefore, she is already familiar with policies, systems, and personnel involved with antimicrobial resistance in the hospital. In this sense, she has already submerged in the environment and her experiences on the topics can be used to triangulate with the findings from this study. Her involvement also allowed

personal reflexivity to be conducted. However, this can lead to a lack of new perspectives and selective reporting bias. The second author who had limited experience on the topic acted as a fresh eye and help with thematic analysis to reduce this limitation. We also did group discussions to minimize the biases and maintain the phenomenology approach in this study. Another limitation is that antibiotics and the pattern of antibiotics used for the treatment of CRE infection in this research were influenced heavily by the National Drug List and the experience of physicians working in the hospital. Hence, other drugs that may have been used in Thailand were not mentioned. This limitation should not significantly affect the data since the treatment of CRE in Thailand was in general homogenous [25,26,28].

In conclusion, physicians realized that CRE resistance was an important problem. However, physicians still did not comply with the CRE treatment guidelines because of the lack of confidence and knowledge in treating CRE infection; insufficient necessary information; and unstandardized ICP practice. Providing accessible necessary information, enough ID specialists, and DUE were reported as solutions for the CRE challenges.

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