The Outcome Of A Carbapenem Stewardship Initiative In A Local Tertiary Teaching Hospital

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ABSTRACT

Carbapenem-resistant isolates have been increasingly reported recently. Carbapenem stewardship is designed to optimize its usage particularly among medical wards with high prevalence of carbapenem prescriptions to combat such emerging resistance. Carbapenem stewardship programmes (CSP) can reduce antibiotic use but clinical outcome of such measures needs further evaluation. We examined this in a prospective manner using feedback mechanism. Our single-center prospective cohort study involved all carbapenem prescriptions across the medical wards (including medical patients admitted to intensive care unit) in a tertiary university hospital setting. The impact of such stewardship was analysed according to the accepted and the rejected groups. The primary endpoint was safety. Safety measure applied in this study was death at Day 30. Secondary endpoints included readmission at day 30, and length of hospitalisation. Over the 19 months' period, input from 144 carbapenem prescriptions was analysed on the basis of acceptance of our CSP recommendations on the use of carbapenem. Recommendations made were as follows: de-escalation of carbapenem; stopping the carbapenem; use for a short duration of 5-7 days; prolonging up to 2 weeks in the case of carbapenem-sensitive Extended Spectrum Beta-Lactamases bacteremia; dose adjustment; and surgical intervention for removal of septic foci. Acceptance rate was 53%. Those who accepted CSP recommendations had no increase in mortality ($p = 0.07$), had a shorter length of hospital stay (LOS) by 6 days and had less readmission rates. Carbapenem stewardship program in the medical wards is safe and does not

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harm the patients with added benefits of reducing the length of hospital stay. However, more time is needed to engage the primary clinical teams by formal clinical presentation and immediate personal feedback by senior Infectious Disease (ID) personnel to increase its acceptance.

INTRODUCTION

In the recent years, the increased use of carbapenem in treating wide spectrum of infectious diseases has raised concern over the potential emergence of carbapenem resistance. Thus, good antibiotic stewardship is essential to optimise the effectiveness of carbapenem use, minimise the toxicity and healthcare cost as well as to limit the emergence resistance[1]. A Singaporean prospective study has demonstrated the usefulness in reducing carbapenem usage and readmission rates. There was no statistical significant change in appropriateness ($p = 0.357$), length of hospital stay ($p = 0.10$), and mortality rates ($p = 0.57$)[2].

Local data has been scarce especially among the teaching hospitals. Carbapenem stewardship was started by an infectious disease physician in 2011 (August) in UKMMC. It involved once weekly table round (every Thursday). Interventions in the form of recommendations included de-escalation, shortening the carbapenem, stopping the carbapenem, and dose adjustment. In 2013, cases started to be posted to "WhatsApp" with patient's particulars, clinical presentation, relevant lab finding, within chat group called "AB Stewards". According to s.40 of the Malaysia Personal Data Protection Act 2010, the processing of such sensitive personal data was allowed for medical purposes provided it was done by a healthcare professional. The acceptance rates ranged from 70 % to 80% (82.5% in 2013, 73.9% in 2014 and 82% in 2015). However, clinical outcomes were not vigorously studied at that time and no published data was available.
Our primary objective was to look at the survival benefit outcome at Day 30 for those involved in this carbapenem stewardship initiative. Our secondary objectives were to compare the outcome of carbapenem stewardship initiative at Day 30 with the following outcomes:-

(a) still in ward;
(b) any readmission? (whether infection-related);
(c) any death (infection-related and non-infection-related)?
(d) any discharge?
(e) length of stay (LOS)

Note: The safety outcomes at 30th day was traced by making the phone call to the respective patients and/or families (if patient has been discharged from the hospital). In the events of readmission to other hospitals, outcomes were traced by calling the respective hospitals or patients/families.

MATERIALS AND METHODS

This was a single centre prospective cohort study conducted in a teaching hospital in Malaysia by the principal investigator (junior medical registrar) along with the help of the pharmacists. The target subjects consisted of all adult patients from a total of seven adult medical wards (a total of 196 beds) and one adult general intensive care unit (only for those under medical team as primary team). The sampling method was in a non-probability manner. The extent of study period was 19 months (July 1, 2015 to January 26, 2017). Those aged 13 years old and above, within one to four days of initiation of carbapenem (including public holidays) were included. The information of these patients at baseline was broadly divided according to the demographic features and clinical features/risk factors.

The minimum sample size required was determined via the following formula:

$$\left(\frac{Z}{MOE}\right)^2 P(1-P)$$

Z= Z value corresponding to the desired confidence interval level; P = Estimated prevalence of the studied population; MOE= Desired margin of error

$$\left(\frac{1.96}{0.05}\right)^2 0.1(0.9)$$

= 138 sample size

All carbapenem cases are identified via three major routes: case note review; pharmacy's system; and pharmacist's notification. For the case note review, the investigator searched in the above wards for cases involving carbapenem prescriptions, depending on the time availability. For the pharmacy's system, the investigator went to the pharmacist's main office to trace the submitted carbapenem prescription forms signed by the respective attending physicians and went to the respective wards to do the stewardship. For the pharmacist's notification, the designated pharmacists of all these medical wards will notify via the electronic notification (i.e. "WhatsApp" application) on the patient's initiation on carbapenem. The feedback form (as shown in Appendix) will be immediately attached to the respective bedside case note, within the 4 days of initiation of carbapenem. The sampling method used was the convenience sampling (nonprobability) due to the limited manpower and time.

Strategy employed in this trial was the audit and feedback mechanism. The indication and inappropriateness of carbapenem usages were judged by the principal investigator alone to ensure data homogeneity using an established set of recommendations. The recommendations encompassed the de-escalation of carbapenem; stopping the carbapenem; use for a short duration of 5-7 days; longer duration (up to 2 weeks) in the case of carbapenem-sensitive Extended Spectrum Beta-Lactamases bacteremia (preliminary culture results were included); the dose adjustment; as well as the surgical intervention for removal of septic foci. The feedback was mainly done in the written form. Whenever possible, the verbal communication was made to the respective medical officer/registrar in charge of the patient. Subsequently, the responses from physician/registrar in charge (accept/reject) within a period of 4 days and at 2 weeks (from the time of initiation) were recorded (if fell on weekend). The data was then compiled and analysed. Cases were reviewed within 4 days of recommendations (if fell on weekend, will be reviewed the next working days). Next review will be 2 weeks from the time of carbapenem initiation due to the limited manpower.

Such data collection had been commenced upon approval of the survey by the Ethics Committee. Finally, the pooled data was analysed applying the SPSS statistical software. P-value of less than 0.05 will be considered as statistically significant in this research.

DEFINITION OF TERMINOLOGIES

Readmission refers to the hosptalization that occurs within 30 days after a discharge (either to UKMMC or to other hospitals).[3-4] Death refers to the mortality during the hospitalisation or within 30 days of the date of discharge. Cause of death in our study was based on the death certificate and/or discharge summary of the relevant patients. Infection-related death was based on the written primary diagnosis of infection (for instance urosepsis), either obtained from the case note or from the death certificate. [5]

The co-morbidities implied in this research encompassed the following :[6] Renal impairment refers to the creatinine level of more than 133 umol/L or doubling of baseline serum creatinine if known[7] (normal range = 62-133 umol/L). Acute liver dysfunction refers to the serum bilirubin level of more than 51umol/l, prothrombin time of more than 60% above normal and a two-fold increase of transaminase level.[8]

Chronic lung disease refers to the disease diagnosed within 1 year prior to admission, for instance, bronchial asthma, chronic obstructive lung disease and lung fibrosis. Diabetes mellitus refers to the fasting blood sugar level of more than 7 mmol/l [9] either in the presence or absence of the oral anti-diabetic agent, or refers to the insulin-dependent patients.

Malignancy in this manuscript was based on the histological diagnosis either in the past or present.

Corticosteroid therapy refers to the dose of 20 mg prednisolone daily for at least two weeks or 30 mg prednisolone daily for at least one week before the positive blood culture.[10]

Neutropenia refers to the absolute neutrophil count of less than 2.5 x 10^6/L. Coagulopathy refers to the thrombocytopenia with a platelet count 100x10^6 /ml, ± a prolonged prothrombin time ±activated partial thromboplastin time more than 80% ± a positive D-Dimer of 1/8 dilution.[11]

RESULTS

A total number of one hundred and forty six patients were identified during the study period. Only two patients were excluded as they discharged at own risk at second day of carbapenem initiation for second opinion. This comprised 51% males (n= 74) and 49% females (n = 70). More than half of them were Malays (63%), followed by Chinese (22%) and India (12%). The other 3% were from the indigenous group and the rest were foreigners (Sudan and Myanmar). Among all these one hundred and forty four patients that were reviewed, the attending physicians only accepted recommendations made to the seventy six patients (53%). The recommendations made to the remaining sixty eight patients were rejected by the attending physician (47%). The baseline characteristics differentiating between the accepted group and the rejected group were as summarized below in Table 1:-

BASELINE CHARACTERISTICS				
Variables	All, n (%)	Accepted Group, n (%)	Rejected Group, n (%)	p Value
Gender				
Male	74 (51.4)	40 (54.1)	34 (45.9)	0.88
Female	70 (48.6)	36 (51.4)	34 (48.6)	
Age	Mean age of 60 +/- 18 years old	Mean age of 57 +/- 19 years old	Mean age of 64 +/- 16 years old	0.02
Number of Co-morbids				
0	17 (11.8)	11 (64.7)	6 (35.3)	Reference Category
1	37 (25.7)	19 (51.4)	18 (48.6)	0.53
2	22 (15.3)	12 (54.5)	10 (45.5)	0.76
> 2	68 (47.2)	34 (50.0)	34 (50.0)	0.41
Nursing Home Residents				
Yes	6 (4.2)	3 (50.0)	3 (50.0)	0.89
No	138 (95.8)	73 (52.9)	65 (47.1)	
Chronic Lung Disease				

Present	22 (15.3)	13 (59.1)	9 (40.9)	0.68
Absent	122 (84.7)	63 (51.6)	59 (48.4)	
Acute Liver Dysfunction				
Exist	9 (6.0)	5 (55.6)	4 (44.4)	0.86
Not	135 (94.0)	71 (52.6)	64 (47.4)	
Coagulopathy				
Present	11 (7.6)	6 (54.5)	5 (45.5)	0.90
Absent	133 (92.4)	70 (52.6)	63 (47.4)	
Renal Impairment				
Yes	61 (42.4)	31 (50.8)	30 (49.2)	0.81
No	83 (57.6)	45 (54.2)	38 (45.8)	
Diabetes				
Yes	66 (45.8)	34 (51.5)	32(48.5)	0.91
No	78 (54.2)	42 (53.8)	36 (46.2)	
Neutropenia				
Exist	10 (6.9)	6 (60.0)	4 (40.0)	0.88
Not	134 (93.1)	70 (52.2)	64 (47.8)	
Malignancy				
Yes	Yes	40 (54.1)	34 (45.9)	0.88
No	No	36 (51.4)	34 (48.6)	
On Chemotherapy				
Yes	11 (7.6)	6 (54.5)	5 (45.5)	0.90
No	133 (92.4)	70 (52.6)	63 (47.4)	
Steroid Use ?				
Yes	8 (5.6)	4 (50.0)	4 (50.0)	0.87
No	136 (94.4)	72 (52.9)	64 (47.1)	

Table 1 : Baseline Variables of Studied Population (Comparison between Cases of Acceptance vs Rejection during Carbapenem Stewardship)

The Table 1 above summarized the similarity in the variables among the accepted group versus rejected group except for the age group (p value > 0.05). Further sub-analysis among the acceptance cases revealed that 53 cases accepted de-escalation (36.81%), 28 cases (19.44%) accepted to use carbapenem for a short duration of 5-7 days, 29 cases (20.14%) used longer duration of carbapenem due to the presence of carbapenem-sensitive Extended Spectrum Beta-Lactamases (ESBL) bacteremia, 32 cases (22.22%) agreed to stop the carbapenem as they were deemed not indicated, and 1 case (0.69%) agreed to adjust the dose of carbapenem (dose reduction for renal adjustment).

Majority of the recommendations were for de-escalation. Among all these cases that refused de-escalation of carbapenem (n = 39), 41% were found to be still in the ward at 30 days. Among all these cases that rejected to de-escalation of carbapenem (n = 39), 41% (16/39 x 100%) was found to be still in the ward at 30 days. The readmission and the infection-related death were noted to higher among those rejected group versus those accepted group, however, the numbers were too small to determine its statistical significance. In those group who accepted to stop the carbapenem, there was no significant difference in the outcomes (i.e. still in ward; readmission; death; discharged). Meanwhile, all the patients (n = 15), whom the carbapenem's duration was shortened according to the recommendation, was 'discharged' when they were reviewed at day 30 ($p< 0.01$). Although the number of readmission was higher among those accepted to continue carbapenem in the case of carbapenem-sensitive ESBL bacteremia, the number (n = 4) was too small to make any statistical conclusion. The readmissions from this group of patients were mainly non infection-related (only 1 case was infection-related but culture negative and the patient was ill).

In the current study, there was neutral survival benefit noted at Day 30 in the recommendations accepted group. A total of seventy four patients in the accepted group as compared to the sixty patients in the rejected group were alive at day 30 ($p = 0.07$). Only two deaths were reported in the accepted group as compared to eight deaths in the rejected group (Table 2).

Several other secondary outcomes had also been identified and outlined below (Table 2) :

Endpoints	Accepted Group n (%)	Rejected Group n (%)	Significance Level, *p*
still in ward	2 (9.1)	20 (90.9)	*p–value <0.01*
30 day readmission	7 (38.9)	11 (61.1)	*Unable to determine the p-value due to small sample sizes*
30 day mortality due to infection	1 (11.1)	8 (88.9)	
30 day mortality not due to infection	1 (100.0)	0 (0.0)	
discharged well	65 (69.1)	29 (30.9)	*p–value < 0.01*
length of stay (LOS)	15.6 ± 7.9 days	21.7 ± 7.5 days	*t value = 4.67, p-value 0.00001 (<0.01)*

Table 2 : Various Secondary Outcomes's Analysis Across the Medical Wards (at 30th day)

DISCUSSIONS

This project has been designed to optimize the carbapenem's prescriptions among our medical wards and ICU medical patients. The medical discipline was chosen due to its high prevalence of such prescription. To our best knowledge, this is the first locally conducted prospective carbapenem-only stewardship project in a university's teaching hospital setting. The core recommendation in our study was based on the prospective audit and feedback strategy as conformed to the guideline set forth in the Infectious Diseases Society of America (IDSA) [12].

Apart from that, the overall acceptance rate of our study was 53%. Table 3 summarized comparisons of acceptance rate among several worldwide studies in terms of methodologies, and interventions for the antibiotic stewardship. The feedback mechanisms of oral recommendations or phone call or direct verbal contact either in French studies or the Singapore study did result in higher acceptance rates (80-90% in French studies and 68% in the Singapore study). Expertise from the infectious disease specialty does play a role to improve the acceptance rate as well, which could possibly explain the higher acceptance rates. One of the obvious observations among all these studies was the involvement of infectious disease specialists in the stewardship program. The prescription review of once weekly in the French study in 2009 might have also allowed non-indicated antibiotic usage to be prolonged for at least 6 days and thus higher acceptance rate.

	Lesprit P, et al (2009) (French) [13]	*Lesprit P, et al (2011) (French)* [14]	*Cosgrove SE, et al (2012) (USA)* [15]	*Lew YX, et al (2015) (Singapore)* [16]	Our Study
Acceptance Rate	80%	90%	66.7%	68%	53%
Nature of Study	Prospective	Prospective	Prospective	Retrospective	Prospective
Frequency of Prescription Review	Prescription review only at day 6	Daily review	Review after 48 hours	Ward pharmacists and Antibiotic Stewardship Programme (ASP) team review the patients from Day 3 of carbapenem use	Prescription review on day 1 itself
Team Member	1 infectious disease	1 full-time infectious	Infectious disease	4 infectious disease	1 general internal

	specialist who provides advice on an on-call basis	disease specialist on an on-call basis	physicians	physicians on rotation (making up 0.5 full-time equivalents daily) and 3 ASP pharmacists	medicine master student
Feedback Mechanism	Recommend-ations to modify the antibiotic regimen were provided orally to the attending physician when appropriate, or were written in the medical chart when direct oral interaction could not occur	Attending physician was called by phone or visited by the infectious disease specialist	The provider was contacted in inappropriate cases	Communicat-ed to the primary care team via documentati-on in the patient's chart and frequently include telephone or in-person discussions	Mainly via documentation in the patient's chart. Direct contact only when possible (limited manpower)
Educational Sessions	Every 6 months, all staff and junior physicians of each ward received education about antibiotic prescribing	Every 6 months, all staff and junior physicians of each ward received education about antibiotic prescribing	None	None	Every 6 to 12 months to master students

Table 3: Antibiotic stewardship studies. Comparisons between our centre and other studies in terms of methodologies, interventions and the acceptance rates for the antibiotic stewardship.

Thus, efforts should be exercised upon increasing the awareness of carbapenem stewardship program, as well as strengthening the educational program on carbapenem stewardship, including continuous medical education (CME), training courses on carbapenem stewardship, and incorporation of such program into the undergraduate medical school curricula. Behavioural change of reluctance to de-escalating antibiotic with the presumption of responding to carbapenem is also something important to be addressed. This is so-called the "physician inertia".

However, as a whole, our study achieved the primary endpoint that carbapenem stewardship is safe. Recommendations in our stewardship project did not influence on the mortality rate. In fact, accepted group had better survival rate although it was not statistically significant. This neutral impact had been demonstrated in several other previous studies[15-18]. On the other hand, the 30-day mortality due to infection was relatively lower in the cases which recommendation was accepted even though the size was too small to be proven statistically. Another positive secondary outcome derived from this study was that of shorter mean hospital stay. This had also been consistently shown in three other studies as well[15-16, 19-20]. This shortening of hospital stay could then be transformed into cost-saving later.

There were a few limitations of our research. Firstly, the sample size was small. Larger samples would have allowed us to have smaller margin of error and to augment the power of the study. Secondly, our current feedback mechanism suffers from the possibilities of not being reviewed in a timely manner or even being ignored. This mechanism may need to be strengthened in the future by engaging directly with the primary team via measures such as direct and immediate verbal feedback; immediate "WhatsApp" to the respective treating physician; designated time for feedback; setting up of pop-ups for lists of inappropriate cases in respective ward's computer; engagement of nurse practitioners and assistants. Thirdly, the method design of reviewing the carbapenem at 2 weeks after the last review at day 4 due to limited manpower. Lastly, the culture of hierarchy and autonomy may have limited our acceptance rate due to the current study was purely run by me as a junior medical registrar for which the recommendations in the carbapenem stewardship could well be ignored by senior highly experienced primary team's physicians. This study again argues the case for a full time infectious disease physician and/or full time infectious disease pharmacist to be involved actively together with like-mindedness senior hospital staff in the stewardship team to help increase the acceptance rate and to conduct meaningful clinical research.

CONCLUSIONS

In conclusion, carbapenem stewardship in the medical patients is safe with added benefits of reducing hospital stay. Acceptance rate was at 53% which may be due to the issues with audit and feedback mechanisms and also lack of confidence with relatively junior staff and on the perception of "just to complete the course as the patient improved" (physician inertia). It underlines a golden opportunity for us to intervene early by creating awareness about the emerging carbapenem-resistant strains and at the same time reassuring them about the safety of compliance to carbapenem

stewardship program, at least in terms of the mortality and the duration of hospital stay. Further studies are required to involve wards of other disciplines to probe into other potential benefits of such stewardship and to develop interventions that are user-friendly.

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REFERENCES

1. Shlaes DM, Gerding DN, John JF Jr, Craig WA, Bornstein DL, Duncan RA, et al. Society for Healthcare Epidemiology of America and Infectious Diseases Society of America Joint Committee on the Prevention of Antimicrobial Resistance: guidelines for the prevention of antimicrobial resistance in hospitals. Infect Control Hosp Epidemiol 1997; 18: 275-291.
2. Seah XF, Ong YL, Tan SW, Krishnaswamy G, Chong CY, Tan NW, et al. Impact of an antimicrobial stewardship program on the use of carbapenems in a tertiary women's and children's hospital, Singapore. Pharmacotherapy 2014; 1-10. [Epub ahead of print]
3. J Valles, J Rello, A Ochagavia, J Garnacho, MA Alcala. Community acquired bloodstream infection in critically ill adult patients. Chest 2003; 123: 1615-24.
4. Silow-Carroll S, Edwards JN, Lashbrook A. Reducing hospital readmissions: lessons from top-performing hospitals. Synthesis report.The Commonwealth Fund 2011;1473(5):1–20.
5. Liew YX, Lee W, Loh JC, Cai Y, Tang SS, Lim CL, et al. Impact of an antimicrobial stewardship programme on patient safety in Singapore General Hospital. Int J Antimicrob Agents 2012; 40 (1):55-60.
6. Petrick P, Kong NC, Nordiah AJ, Cheong IK, Tamil MA. Outcome of bacteraemia in patients admitted to the adult medical wards of the UKM hospital. Med J Malaysia 2007; 62(4):329-334.
7. Anderson RJ, Linas SL, Berns AS, Henrich WL, Miller TR, Gabow PA, et al. Nonoliguric acute renal failure. N. Engl. J, Med 1977; 296:1134-1138.
8. Tran DD, Groeneveld AB, Van der Meulen J, Nauta JJ, Strack van Schijndel RJ, Thijs LG. Age, chronic disease, sepsis, organ system failure and mortality in a medical intensive care unit. Crit Care Med 1990; 18 (5):474-479.
9. Bagdade JD, Nielson KL. Reversible abnormalities in phagocytic function in poorly controlled diabetic patients. Am J Med Sci 1972; 263:451-456.
10. Axelrod L. Glucocorticoid therapy. Medicine 1976; 55:39-65.
11. Bick RL, Baker WF Jr. Disseminated intravascular coagulation syndromes. Hematol Pathol 1992; 6: 1-24.
12. Tamar FB, Sara EC, Lilian MA, Conan M, Audrey NS, Edward JS, et al. Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America.Clin Infect Dis2016; 62 (10): e51-e77.

13. Lesprit P, Duong T, Girou E, Hemery F, Brun-Buisson C. Impact of a computer-generated alert system prompting review of antibiotic use in hospitals. J Antimicrob Chemother 2009; 63(5): 1058–1063.
14. Lesprit P, Merabet L, Fernandez J, Legrand P, Brun-Buisson C. Improving antibiotic use in the hospital: Focusing on positive blood cultures is an effective option. Presse Med 2011; 40 (6): e297-303.
15. Cosgrove SE, Seo SK, Bolon MK, Sepkowitz KA, Climo MW, Diekema DJ, et al. CDC Prevention Epicenter Program. Evaluation of postprescription review and feedback as a method of promoting rational antimicrobial use: a multicenter intervention. Infect Control Hosp Epidemiol 2012; 33(4): 374-80.
16. Lew KY, Ng TM, Tan M, Tan SH, Lew EL, Ling LM, et al. Safety and clinical outcomes of carbapenem de-escalation as part of an antimicrobial stewardship programme in an ESBL-endemic setting. J Antimicrob Chemother 2015; 70(4): 1219-25.
17. Delory T, De Pontfarcv A, Emirian A, About F, Berdougo B, Brun-Buisson C, et al. Impact of a program combining pre-authorization requirement and post-prescription review of carbapenems: an interrupted time-series analysis. Eur J Clin Microbiol Infect Dis 2013; 32(12): 1599-1604.
18. Davey P, Marwick CA, Scott CL, Charani E, McNeil K, Brown E, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database Syst Rev. 2017 Feb 9;2:CD003543. [Epub ahead of print]
19. Liew YX, Lee W, Loh JC, Cai Y, Tang SS, Lim CL, et al. Impact of an antimicrobial stewardship programme on patient safety in Singapore General Hospital.Int J Antimicrob Agents 2012; 40 (1): 55-60.
20. Loo LW, Liew YX, Lee W, Chlebicki P, Kwa AL. Impact of antimicrobial stewardship program on outcomes in patients with acute bacterial skin and skin structure infections (ABSSSIs) in an acute-tertiary care hospital. Infect Dis Ther 2015; 4 (suppl 1): 15-25.
21. Gentry CA, Greenfield RA, Slater LN, Wack M, Huycke MM. Outcomes of an antimicrobial control program in a teaching hospital. Am J Health Syst Pharm 2000; 57 (3): 268-274.