Received: 30 June 2020 | Revised: 12 August 2020 | Accepted: 17 August 2020

DOI: 10.1111/jcpt.13265

ORIGINAL ARTICLE

Journal of Clinical Pharmacy and Therapeutics WILEY

Clinical pharmacy interventions in intensive care unit patients

Li-Huei Chiang MS[1] | Ya-Lien Huang MS[1] | Tzu-Cheng Tsai MS[1,2]

[1]Department of Clinical Pharmacy Service, Linkou Chang Gung Memorial Hospital, Taoyuan, Taiwan

[2]Department of Long Term Care, Hsin Sheng Junior College of Medical Care and Management, Taoyuan, Taiwan

Correspondence
Li-Huei Chiang, Department of Clinical Pharmacy Service, Linkou Chang Gung Memorial Hospital, Taoyuan, Taiwan.
Email: lindseychiang@gmail.com

Abstract

What is known and objective: The drug therapy of critically ill patients requires intensive evaluation and management due to their severity of illness. These patients often require complex medication regimens. This study analysed the pharmaceutical care provided by clinical pharmacists (CPs) in a single medical centre in Taiwan. In addition, we explored the drug-related problems (DRPs) experienced by patients in intensive care units (ICUs) to determine how to improve the quality and safety of drug therapy.

Methods: This retrospective study was conducted from February 2019 to January 2020. The CPs implemented Taiwan's National Health Insurance (NHI) Scheme for Improving Hospital Drug Safety and Quality programme to improve the safety and quality of drug therapy. The CPs included in the study had at least 2 years' clinical experience and had participated in an ICU team for at least 6 consecutive months. They provided individualized drug treatment evaluation and intervention. Content of care was documented in the Clinical Pharmacy Service Record.

Results and discussion: A total of 4374 pharmacy care records were evaluated by 12 CPs. The major category of ICU pharmaceutical care was medication reconciliation (n = 2938; 67.2%). Most of the medication interventions were for errors in dosing or dosing frequency (n = 218; 55.8%). Patients with renal dysfunction required more pharmaceutical interventions than did patients with normal renal function (odds ratio = 1.63; 95% confidence interval 1.31-2.01). The main interventions were related to antimicrobial agents (n = 386; 81.3%). During the study period, 99.2% of interventions were accepted and 90.8% were changed within 24 hours.

What is new and conclusion: Increased pharmaceutical interventions for patients with renal dysfunction compared with patients with normal renal function were observed. Most cases of inappropriate frequency of dosing or dosing of antimicrobial agents required intervention.

KEYWORDS

clinical pharmacist, drug-related problem, intensive care unit, pharmaceutical care, renal insufficiency

1 | WHAT IS KNOWN AND OBJECTIVE

A systematic review and meta-analysis revealed that pharmacist participation in multidisciplinary treatment teams can improve the patient outcomes by reducing mortality rate, the length of stay in intensive care units (ICUs), and adverse drug events (ADEs).[1] Due to severity of illness and major changes in organ function, critically ill patients have complex and changing pharmacokinetics and pharmacodynamics, requiring careful evaluation and drug therapy management. Considerable evidence supports the value of having

clinical pharmacists (CPs) in ICUs during multidisciplinary critical care.[2-9] In addition, numerous pharmaceutical economics studies have shown that pharmaceutical intervention can lead to cost savings.[10-18]

Medication is the most common type of treatment in ICUs and is often associated with adverse events. Critically ill patients always receive complex medication regimens. The incidence of preventable and potential ADEs in ICUs is twice as high as in other units. Even after adjustment for order of drug administration, the probability of preventable and potential ADEs in ICUs was shown by one study to still be greater than that in other units.[19] Compared with patients in general wards, ICU patients were 16, 3, and 2 times more likely to experience ADEs related to treatments for kidney injury, thrombocytopenia, and emergency ICU admission, respectively.[20]

This study evaluated the clinical pharmacy care and drug-related problems (DRPs) in the ICU of a single medical centre in Taiwan. We identified patients at high risk for DRPs to determine how to improve the safety and quality of medication administration.

2 | METHODS

2.1 | Study design and setting

This retrospective study was conducted from February 2019 to January 2020 in a medical centre with approximately 250 adult ICU beds. The pharmaceutical care records of adult patients (older than 18 years) were evaluated. The multidisciplinary critical care teams included specialist physicians, nurses, CPs, respiratory therapists, rehabilitation specialists, social workers, and dieticians. The CPs participated in the multidisciplinary critical care and ensured the rational drug prescription and administration.

The clinical pharmacy care process was as follows: (a) information related to patient treatment was accessed from electronic medical records. (b) The CPs assessed ensured the rationality of drug prescriptions, evaluated the risk of drug interactions and ADEs, and monitored drug efficacy according to doctors' diagnoses and care plans. (c) The CPs participated in multidisciplinary care and proposed plans for drug efficacy monitoring. (d) The CPs provided drug consultation services, consisting of the provision of guidance to inpatients and medical staff. (e) The CPs made suggestions for the improvement of therapeutic efficacy.

2.2 | CP qualifications

The CPs who executed Taiwan's National Health Insurance Scheme for Improving Hospital Drug Safety and Quality had to meet the following qualifications: (a) possession of a pharmacist licence with at least 2 years of cumulative clinical experience and (b) participation in an ICU team for at least 6 consecutive months, as evidenced by critical care or equivalent clinical pharmacy care service records (at least 10 per month). After passing the qualification review, the CPs provided individualized evaluations of patients' medical treatments, interventions and follow-up.

Intensive pharmacy care fees were calculated by patient day. In addition, the direct effects of pharmaceutical interventions on treatment cost were considered. The cost savings for the interventional drugs were classified as *increase*, *no difference* and *reduction*.

2.3 | Pharmaceutical interventions

The content of care was documented in the Clinical Pharmacy Service Record. Documentation was made in accordance with the SOAP (Subjective, Objective, Assessment, and Plan) note, and CP decisions were divided into two groups. (a) In the intervention group, the CPs gave further recommendations or guidance on medication after evaluation. (b) In the non-intervention group, after evaluation, the original treatment was maintained, with no further recommendations or guidance offered.

We analysed risk factors related to pharmaceutical interventions by CPs and compared the variables between the two groups, including age, gender, length of ICU stay, and special groups. Special group analysis included elderly patients and patients with renal, liver, or combined liver–kidney dysfunction.

2.4 | Statistical analysis

Data collection and statistical analysis were performed using Excel 2013 and SAS software, Enterprise Guide 5.1 (SAS Institute Inc, Cary, NC, USA). The pharmacy care records were supplemented by the electronic medical record system. Continuous variables were expressed as means and standard deviations (mean ± standard deviation). Student's *t* test was used for continuous variables, and the chi-square test or Fisher's exact test was used for categorical variables for comparison of between-group differences. A two-tailed *P* value < .05 was considered statistically significant.

3 | RESULTS

The pharmacy care records of 4373 patients admitted to ICU between February 2019 and January 2020 were reviewed (Figure 1). The average age was 64.0 ± 16.5 years (18-104 years; Figure 2). Of the patients, 2833 (64.8%) were male. The average length of ICU stay was 17.0 ± 16.6 days (1-377 days). The special group comprised 2848 patients (65.1%), including 2,377 (53.4%) older than 65 years, 1350 (30.9%) with renal dysfunction, 116 (2.7%) with liver dysfunction and 231 (5.3%) with combined liver–kidney dysfunction (Table 1).

Over the study period, 12 CPs created a total of 4374 pharmacy care records of 391 interventions. A total of 12 036 person days (an average of 2.8 person days per record) of intensive pharmacy care

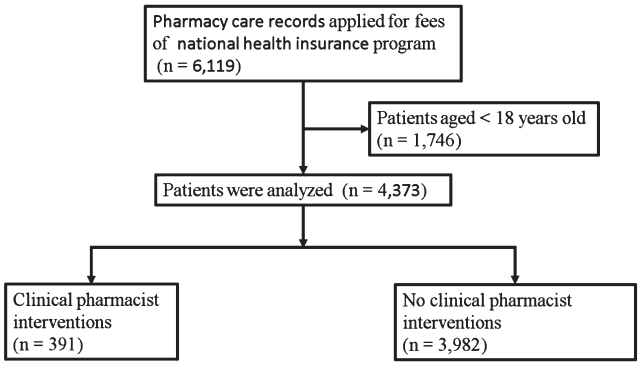

FIGURE 1 Flow chart of the patient selection process for pharmaceutical intervention by clinical pharmacists

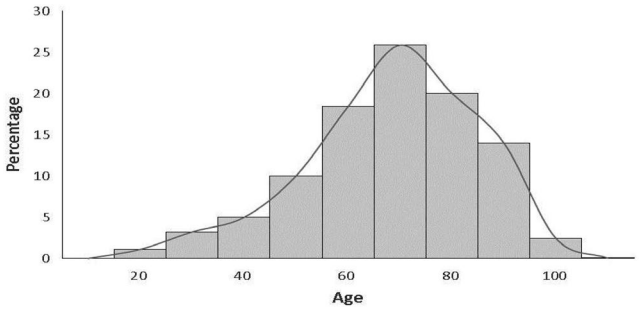

FIGURE 2 Distribution of pharmacy care records by age (n = 4373)

fees were applied, classified into four types: 2938 medication reconciliations (67.2%), 928 monitoring recommendations (21.2%), 409 proactive suggestions (9.4%) and 98 prescription recommendations (2.2%).

Patients with longer ICU stays required more pharmaceutical interventions ($P < .05$). The top five intervention classifications were inappropriate drug frequency or dosing (n = 218, 55.8%), discontinuation of drug therapy (n = 65, 16.6%), changes in drug therapy (n = 46, 11.8%), indicated drug not prescribed (n = 34, 8.7%) and therapeutic drug monitoring (n = 17, 4.3%; Figure 3). During the study period, 388 interventions (99.2%) were accepted and 90.8% were changed within 24 hours.

The number of pharmaceutical interventions in the special group was 1.55 times that in the non-special groups ($P = .002$, 95% confidence interval [CI] 1.23-1.96). The number of interventions required for patients with renal dysfunction was 1.63 times higher than that for patients with normal renal function ($P < .0001$, 95% CI 1.31-2.01). The classification of the interventional drugs included the following: 386 antimicrobial agents (81.3%), 15 anticoagulants/antiplatelet agents (3.2%) and 14 central nervous system agents (2.9%; Table 2). Among the antimicrobial agents, glycopeptides (25.8%) and carbapenems (20.9%) were most frequently used (Figure 4). With regard to economic effects, 41.9% of cases increased the cost of interventional drugs, 48.6% reduced the cost, and the rest had no effect. In interventions evaluated as immediate cost increases, additional medication treatment or increased doses were recommended. Of the interventions evaluated as direct cost reductions, 36% were due to termination of drug therapy.

4 | DISCUSSION

This retrospective study was conducted to evaluate the effects of CP participation in a multidisciplinary ICU team. Pharmaceutical interventions refer to a series of actions in which CPs provide patient-centred care, make recommendations, and prevent or resolve DRPs. These interventions differ from CPs' routine drug review task. Before the CPs submit a proposal, they must evaluate a patient's overall clinical status; moreover, they must stay abreast of the latest clinical developments. Consequently, participation in such ICU teams is more time-consuming and expensive for CPs than is performing than routine drug reviews.

Twelve CPs are responsible for about 300 ICU patients. On average, each CP has 1-4 wards of responsibility, but he or she could only participate in one multidisciplinary round every day. According to our regulations, there should be at least one written pharmacy record when the patient stays in the ICU. Since the ICU length of stay varied, some even as short as a few hours for postoperative

TABLE 1 Characteristics of patients in the intervention group and non-intervention group

Characteristics	Intervention group (n = 391)	No intervention group (n = 3982)	*P*-value
Age, mean years ± SD (range)	63.9 ± 17.0 (18-98)	64.0 ± 16.4 (18-104)	.9295
Male sex, n (%)	254 (65.0)	2579 (64.8)	.9385
Length of ICU stay, mean days ± SD (range)	20.0 ± 14.5 (2-107)	17.8 ± 16.8 (1-377)	.0061
Special group, n (%)	288 (73.7)	2560 (64.3)	.0002
Elder, n (%)	217 (55.5)	2120 (53.2)	.3928
Renal dysfunction, n (%)	160 (40.9)	1190 (29.9)	<.0001
Liver dysfunction, n (%)	11 (2.8)	105 (2.6)	.8359
Combined liver-kidney dysfunction, n (%)	21 (5.4)	210 (5.3)	.9347

Abbreviations: SD, standard deviation.

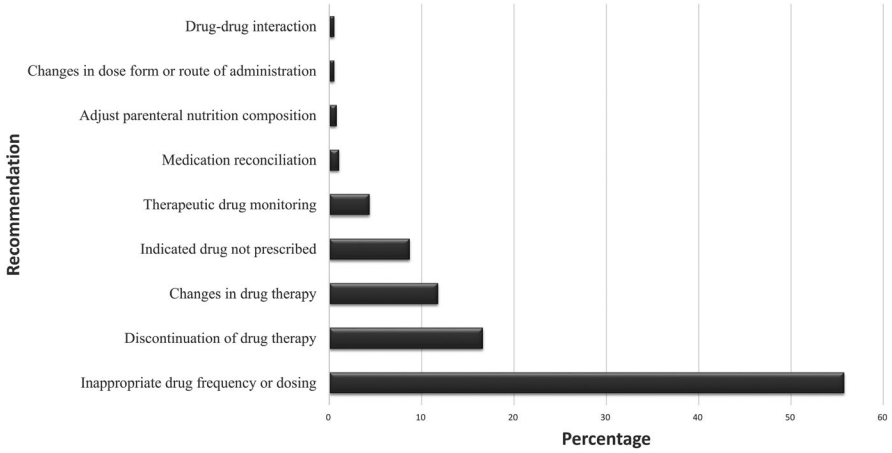

FIGURE 3 Distribution of pharmaceutical interventions provided by clinical pharmacists in intensive care units (n = 391)

TABLE 2 Categories of medications with drug-related problems requiring pharmaceutical intervention by the clinical pharmacists in intensive care units

Categories	Number	%
Antimicrobial agents	386	81.3
Anticoagulants/antiplatelet agents	15	3.2
Central nervous system agents	14	2.9
Cardiovascular agents	11	2.3
Electrolytes and agents for caloric/water Balance	11	2.3
Gastrointestinal agents	9	1.9
Psycholeptics	4	0.8
Anaesthetics	4	0.8
Corticosteroids	4	0.8
Antihistamines	4	0.8
Miscellaneous medications	13	2.7

observation, the number of non-intervention records is high and the actual ratio of CP intervention is only 8.94%. These interventions potentially prevented harm to patients that would have prolonged their hospital stay or caused permanent disability or injury.

A systematic review of 38 studies indicated risk factors for DRPs requiring CP intervention. These risk factors were as follows: prescription of certain drugs or drug categories; advanced age (older than 65 years); being female; renal dysfunction; and liver dysfunction. The most common DRPs were related to medications such as intravenous antimicrobial agents, thrombolytics/anticoagulants, cardiovascular drugs, central nervous system drugs. The results of our research were similar. This review article found that no study discussed risk factors related to the need for pharmacists' interventions. This may be due to not having had sufficient evidence to support a finding that pharmaceutical interventions were associated with reduced ADEs.[21]

Approximately 30.9% of the patients in our study had renal insufficiency. Such patients often need to receive lower doses of drugs than do patients with normal renal function. Patients with risk of renal dysfunction were classified into three groups: high risk, hidden risk and normal risk. Among patients with hidden risk, prescription errors mainly involved incorrect dosage. Antibiotics contributed to most DRPs. Drug safety can be improved through more accurate assessment of renal function and prescribing an appropriate dosage for renal drug clearance.[22]

A study stated that errors in drug combination, frequency of administration, and dose are the three most common DRPs in ICUs.[23]

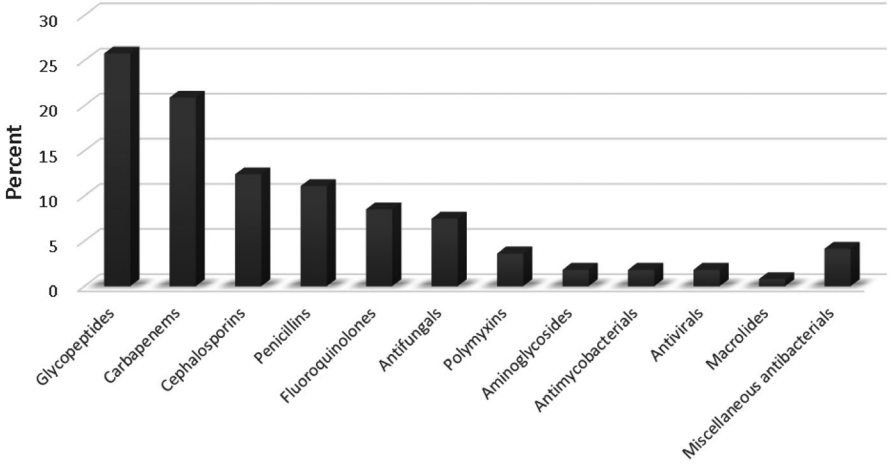

FIGURE 4 Categories of antimicrobial agents with drug-related problems requiring pharmaceutical intervention by clinical pharmacists of intensive care units

Another study found that the main type of CP intervention is adjusting an inappropriate dosage.[24] Our results showed that the leading cause of CP intervention was inappropriate dosing or dosing frequency. Establishing the optimal dose regimen for critically ill patients is a considerable challenge. Many such patients have unstable clinical conditions, including kidney and liver failure. Therefore, dosage may require frequent adjustment. In these cases, CPs can dispense medication-related advice.

The drugs most commonly used in our pharmaceutical interventions were antimicrobial agents. As patients become more ill and require ICU admission, the proper use of antimicrobial agents is critical. The CPs applied the principles of pharmacokinetics and pharmacodynamics to clinical practice in evaluation of bacterial drug resistance in ICU patients and selection of appropriate antimicrobial agents.[25] Following initiation of drug therapy, the CPs assessed possible toxicity or side effects. Timely adjustment to dosing was performed on the basis of patients' organ function, especially that of the kidneys.

Among the patients in the intervention group, 40.9% had renal dysfunction. They were classified as high risk for DRPs in ICUs. Patients with renal dysfunction required considerably more pharmaceutical interventions than did patients with normal renal function. With regard to age or gender, no difference between the intervention and non-intervention groups was found. The second and third most common reasons for pharmaceutical interventions were discontinuation of drug therapy and changes in drug therapy. The interventions highlighted the importance of medication reconciliation, which improves treatment safety and simultaneously reduces unnecessary drug costs.

5 | WHAT IS NEW AND CONCLUSIONS

The renal function of critically ill patients can deteriorate or improve rapidly. Medication use should be recommended on the basis of a patient's overall clinical status as evaluated by a CP. Patients with renal dysfunction required substantially more pharmaceutical intervention than did patients with normal renal function, and in many cases, the dosing frequency of antimicrobial agents required adjustment.

ACKNOWLEDGEMENT

The grant was supported by Chang Gung Memorial Hospital.

CONFLICT OF INTEREST

All authors have no financial or other conflicts of interest.

ETHICAL APPROVAL

This study was approved by Institutional Review Board of Chang Gung Medical Foundation (IRB No.: 202000781B0).

ORCID

Li-Huei Chiang https://orcid.org/0000-0002-0876-7877

REFERENCES

1. Lee H, Ryu K, Sohn Y, Kim J, Suh GY, Kim E. Impact on patient outcomes of pharmacist participation in multidisciplinary critical care teams: a systematic review and meta-analysis. *Crit Care Med*. 2019;47(9):1243-1250.
2. Ho CK, Mabasa VH, Leung VW, Malyuk DL, Perrott JL. Assessment of clinical pharmacy interventions in the intensive care unit. *Can J Hosp Pharm*. 2013;66(4):212-218.
3. Martins RR, Silva LT, Lopes FM. Impact of medication therapy management on pharmacotherapy safety in an intensive care unit. *Int J Clin Pharm*. 2019;41(1):179-188.
4. Kessemeier N, Meyn D, Hoeckel M, Reitze J, Culmsee C, Tryba M. A new approach on assessing clinical pharmacists' impact on prescribing errors in a surgical intensive care unit. *Int J Clin Pharm*. 2019;41(5):1184-1192.
5. Krzyzaniak N, Bajorek B. A global perspective of the roles of the pharmacist in the NICU. *Int J Pharm Pract*. 2017;25(2):107-120.
6. Hisham M, Sivakumar MN, Veerasekar G. Impact of clinical pharmacist in an Indian intensive care unit. *Indian J Crit Care Med*. 2016;20(2):78-83.
7. Fideles GM, de Alcântara-Neto JM, Peixoto Júnior AA, et al. Pharmacist recommendations in an intensive care unit: three-year clinical activities. *Rev Bras Ter Intensiva*. 2015;27(2):149-154.
8. Erstad BL, Haas CE, O'Keeffe T, Hokula CA, Parrinello K, Theodorou AA. Interdisciplinary patient care in the intensive care unit: focus on the pharmacist. *Pharmacotherapy*. 2011;31(2):128-137.
9. Klopotowska JE, Kuiper R, van Kan HJ, et al. On-ward participation of a hospital pharmacist in a Dutch intensive care unit reduces prescribing errors and related patient harm: an intervention study. *Crit Care*. 2010;14(5):R174.
10. Leache L, Aquerreta I, Aldaz A, Monedero P, Idoate A, Ortega A. Clinical and economic impact of clinical pharmacist interventions regarding antimicrobials on critically ill patients. *Res Soc Admin Pharm*. 2020;16(9):1285-1289.
11. Mahmoudi L, Mohammadi R, Niknam R. Economic impact of pharmacist interventions on correction of stress-related mucosal damage prophylaxis practice. *Clinicoecon Outcomes Res*. 2019;11:111-116.
12. Gammie T, Vogler S, Babar ZU. Economic evaluation of hospital and community pharmacy services. *Ann Pharmacother*. 2017;51(1):54-65.
13. Yen YH, Chen HY, Wuan-Jin L, Lin YM, Shen WC, Cheng KJ. Clinical and economic impact of a pharmacistmanaged i.v.-to-p.o. conversion service for levofloxacin in Taiwan. *Int J Clin Pharmacol Ther*. 2012;50(02):136-141.
14. Saokaew S, Maphanta S, Thangsomboon P. Impact of pharmacist's interventions on cost of drug therapy in intensive care unit. *Pharm Pract*. 2009;7(2):81-87.
15. Lee AJ, Boro MS, Knapp KK, Meier JL, Korman NE. Clinical and economic outcomes of pharmacist recommendations in a Veterans Affairs medical center. *Am J Health Syst Pharm*. 2002;59(21):2070-2077.
16. Nesbit TW, Shermock KM, Bobek MB, et al. Implementation and pharmacoeconomic analysis of a clinical staff pharmacist practice model. *Am J Health Syst Pharm*. 2001;58(9):784-790.
17. Torgerson DJ, Campbell MK. Economics notes: cost effectiveness calculations and sample size. *BMJ*. 2000;321(7262):697.
18. De Rijdt T, Willems L, Simoens S. Economic effects of clinical pharmacy interventions: a literature review. *Am J Health Syst Pharm*. 2008;65(12):1161-1172.
19. Cullen DJ, Sweitzer BJ, Bates DW, Burdick E, Edmondson A, Leape LL. Preventable adverse drug events in hospitalized patients: a comparative study of intensive care and general care units. *Crit Care Med*. 1997;25(8):1289-1297.

20. Kane-Gill SL, Kirisci L, Verrico MM, Rothschild JM. Analysis of risk factors for adverse drug events in critically ill patients*. *Crit Care Med*. 2012;40(3):823-828.
21. Suggett E, Marriott J. Risk factors associated with the requirement for pharmaceutical intervention in the hospital setting: a systematic review of the literature. *Drugs Real World outcomes*. 2016;3(3):241-263.
22. Fields W, Tedeschi C, Foltz J, et al. Reducing preventable medication safety events by recognizing renal risk. *Clin Nurse Spec*. 2008;22(2):73-78.
23. Agalu A, Ayele Y, Bedada W, Woldie M. Medication prescribing errors in the intensive care unit of Jimma University Specialized Hospital, Southwest Ethiopia. *J Multidiscip Healthc*. 2011;4:377-382.
24. Reinau D, Furrer C, Stämpfli D, Bornand D, Meier CR. Evaluation of drug-related problems and subsequent clinical pharmacists' interventions at a Swiss university hospital. *J Clin Pharm Ther*. 2019;44(6):924-931.
25. Lodise TP, Drusano GL. Pharmacokinetics and pharmacodynamics: optimal antimicrobial therapy in the intensive care unit. *Crit Care Clin*. 2011;27(1):1-18.

How to cite this article: Chiang L-H, Huang Y-L, Tsai T-C. Clinical pharmacy interventions in intensive care unit patients. *J Clin Pharm Ther*. 2020;00:1–6. https://doi.org/10.1111/jcpt.13265