Medication-related Problems in Intensive Care Unit Survivors: Learning from a Multicenter Program

Few data measure the problems critically ill patients have with medications after hospital discharge, which medications are involved, and how severe the consequences are (1–3). We sought to assess the prevalence and severity of medication-related problems in intensive care unit (ICU) survivors and explore pain management strategies. We did so among patients attending a five-site post-ICU program in Scotland between September 2016 and June 2018.

Methods

Ethical approval was granted by the North West (Liverpool Central) Research Ethics Committee (reference number: 17/NM/0199). All patients provided written consent.

Intensive Care Syndrome: Promoting Independence and Return to Employment (InS:PIRE) is a 5-week rehabilitation program for ICU survivors. Previous research has described this program (4–6). Participants were invited between 4 and 12 weeks after hospital discharge. Patients were eligible if they received level three care or more than 7 days of level two care. U.K. level three patients require multiple organ support or invasive respiratory support alone. Level two patients require single organ support or postoperative care (7). Patients who were otherwise deemed high risk were invited (for example, one patient who received noninvasive ventilation for a prolonged duration was invited), as were self-referred patients.

A pharmacist provided a standardized review for all patients that included medicine reconciliation, assessment of medication appropriateness, identification of problems, assessment of adherence, and provision of education. Prescribed medications were documented at the following four time points: before ICU admission, at ICU discharge, at hospital discharge, and InS:PIRE (at the start of the program). Data were gathered from primary care and in-hospital notes and the patient and caregiver. Standardization across sites was ensured by one-to-one training, regular multisite meetings, and the availability of a website with instructional materials. There was no standardized pharmacy pre–hospital discharge intervention or medicine reconciliation provided across the sites involved.

The type of medication-related problem was categorized using a modified version of the Hepler and Strand framework (8). Categories of problems, alongside an example of each, are provided in the online supplement. The significance of these problems was classified using Blix's scale (9). A problem that had a significance rating of 1 was deemed low risk, a significance rating of 2 was deemed moderate risk, a significance rating of 3 was deemed major risk, and a significance rating of four was deemed potentially catastrophic. For a detailed breakdown of the Blix scoring system, see the online supplement. Scores of 2 or more were deemed clinically significant. Associated clinical factors and pharmacy recommendations were collated, and the significance of the problem was independently scored by two clinicians. The drugs involved were categorized according to their British National Formulary classification (10).

McNemar's test was used to compare the difference between patients who were prescribed analgesia before admission and those who were prescribed analgesia during the InS:PIRE visit. Pearson's χ^2 test was used to compare post-ICU opioid prescribing. Logistic regression determined whether demographic factors were associated with clinically significant medication-related problems. An unadjusted model was generated; variables with P values of less than 0.1 or clinically significant P values (age, severity of illness, and length of exposure) were used to create the adjusted model. IBM SPSS Statistics 24 was used (11).

Results

A total of 253 patients attended InS:PIRE across five sites. A total of 183 patients had a documented pharmacy review and provided consented. Baseline demographics are shown in Table 1.

The median number of medications prescribed was 5 (interquartile range [IQR], 3–9) before ICU admission, 6.5 (IQR, 4–9) at ICU discharge, 7 (IQR, 5–10) at hospital discharge, and 6 (IQR, 4–9) at InS:PIRE. Patients were prescribed a total of 1,216 medications at InS:PIRE; 171 were associated with a medication-related problem, and 27 necessary medications had been omitted (a total of 198 problems).

A total of 115 patients (62.8%) required at least one pharmacy intervention, such as clarifying the duration of treatment ($n = 44$), followed by educating ($n = 33$), and correcting drug omissions ($n = 27$). Twenty-seven pharmacy interventions were classified as minor, 141 were classified as moderate, and 30 were classified as severe. Thus,

Table 1. Baseline demographics of InS:PIRE participants

Characteristic	Cohort ($n = 183$)
Sex, M, *n* (%)	97 (56.3)
Age, yr, median (IQR)	58 (50–65)
ICU LOS, d, median (IQR)	12 (7–19)
Hospital LOS, d, median (IQR)	28 (16–47)
APACHE II, median (IQR)	20 (15–25)
SIMD decile, median (IQR)*	3 (1–6)
Patients ventilated, *n* (%)	159 (86.9)
Duration, d, median (IQR)	8 (4–14)
Patients requiring RRT, *n* (%)	35 (19.1)
Duration, d, median (IQR)	7 (2–12)
Patients requiring multiple vasoactive drugs, *n* (%)	90 (49.2)
Duration, d, median (IQR)	3 (1–7)
Medical diagnosis, *n* (%)	112 (61.2)
Surgical diagnosis, *n* (%)	71 (38.8)

Definition of abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; ICU = intensive care unit; InS:PIRE = Intensive Care Syndrome: Promoting Independence and Return to Employment; IQR = interquartile range; LOS = length of stay; RRT = Renal Replacement Therapy; SIMD = Scottish Index of Multiple Deprivation.
*The SIMD is a measure of socioeconomic deprivation; decile 1 represents the most deprived and decile 10 represents the most affluent (21).

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86.4% ($n = 171$) were clinically significant. A breakdown, together with examples of the severe interventions, is shown in Table 2.

Neurological drugs were the most commonly problematic ($n = 65$), including analgesic ($n = 45$) (e.g., tramadol and dihydrocodeine) and psychiatric medications ($n = 20$) (e.g., sertraline); a majority of these were new medications prescribed at or after ICU (55.4%; $n = 36$). Cardiovascular ($n = 40$), gastrointestinal ($n = 34$), and nutritional ($n = 25$) medications were other common problematic classes.

Before the ICU, 33.3% of patients ($n = 61$) were prescribed regular analgesia; this increased to 60.7% ($n = 111$) at InS:PIRE, an absolute increase of 27.4% (95% confidence interval [CI], 20.2–34.4%; $P < 0.001$). Similarly, 22.4% ($n = 41$) of patients were prescribed a regular opioid pre-ICU compared with 38.7% ($n = 71$) at InS:PIRE, an absolute increase of 16.3% (95% CI, 9.8%–22.8%; $P < 0.001$). There was not a significant difference between the use of opiates between surgical and medical admissions ($P = 0.445$).

Logistic regression was used to explore if clinical demographics predicted a clinically significant medication-related problem. The adjusted model included age, ICU length of stay, hospital length of stay, Acute Physiology and Chronic Health Evaluation II, number of days of Renal Replacement Therapy, number of days of ventilation, the number ICU discharge medications and the World Health Organization analgesia classification at InS:PIRE (Table 3) The unadjusted analysis can be found in the online supplement.

Table 3. Results of multivariable logistic regression

Variable	Adjusted Logistic Regression		
	OR	95% CI	*P* Value
Age	0.99	0.96–1.02	0.55
ICU LOS	0.95	0.89–1.02	0.14
Hospital LOS	**1.03**	**1.01–1.05**	**0.02**
APACHE II	1.04	0.99–1.10	0.16
Days of Renal Replacement Therapy	1.03	0.94–1.14	0.51
Days of ventilation	1.04	0.97–1.11	0.29
Number of ICU discharge medications	**1.15**	**1.04–1.28**	**0.01**
WHO classification at InS:PIRE	—	—	—
No analgesia	1	—	—
Step 1*	2.02	0.84–4.86	0.12
Step 2*	**5.20**	**2.07–13.20**	**0.001**
Step 3*	1.95	0.61–6.26	0.26

Definition of abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; CI = confidence interval; ICU = intensive care unit; InS:PIRE = Intensive Care Syndrome: Promoting Independence and Return to Employment; LOS = length of stay; OR = odds ratio; WHO = World Health Organization.
Bold values represent significant results.
*Step 1 is nonopioid analgesia for mild pain (e.g. paracetamol), step 2 is weak opioid analgesia for mild to moderate pain (e.g., codeine), and Step 3 is strong opioid analgesia for moderate to severe pain (e.g., morphine) (22).

Discussion

This multicenter study has demonstrated that over 60% of ICU patients have issues with medicines in the post–hospital discharge period, with a large proportion of these issues related to psychiatric and pain medications. Longer durations of ICU treatment and complex ICU discharge prescriptions were identified as risk factors for a medication-related problem.

Table 2. A breakdown and examples of the severe interventions undertaken

Severe Medication Interventions ($n = 30$)	Clinical Example
Drug omissions ($n = 11$)	Prophylactic antibiotics not restarted in a splenectomy patient
Adverse event ($n = 2$)	Intolerable side effects from Pregabalin commenced during admission resulting in nonadherence and poor pain management
New treatment recommendation ($n = 1$)	Omeprazole initiated for Aspirin-related melaena
Dose increase ($n = 3$)	Titrate gabapentin to pre–hospital admission dose to treat ongoing neuropathic pain
Dose decrease ($n = 2$)	Theophylline dose increased during admission, symptoms of toxicity at clinic, level checked, and dose decreased
Clarification of treatment duration ($n = 5$)	Morphine commenced during admission, plan made with patient to reduce and stop
Education ($n = 5$)	Nonadherence with apixiban, patient was unaware of why it had been started
Monitoring/Referral ($n = 2$)	Patient on 5 analgesics with poorly controlled pain, referred to the chronic pain team

These results are contextualized by evidence that providing a pharmacy review at transitions of care can improve safety and reduce 30-day hospital readmission in patients with heart failure and primary care patients (12, 13). Similarly, a recent study has shown that a pharmacy review as part of a bundled approach to care may reduce long-term mortality in the group with sepsis (14). More research is required to understand the potential of this intervention and how to integrate it within the complexities of ICU care. We would recommend, based on our learning, that a medicines reconciliation exercise should be used at all transitions of care for this group of patients, especially at hospital discharge. A clear plan for escalation and de-escalation of medicines should also be made, which should be shared with patients and ongoing care providers across the recovery arc.

Our findings contrast with a recent Canadian study that demonstrated that opiate use did not increase after critical illness (15). This may be explained by differences in how data was collected between these studies (in person vs. retrospective electronic health records) and the time points at which opioid use was measured. Other work has focused on medication issues after critical illness and has shown a high rate of unintentional continuation of antipsychotics (16). However, inappropriate drug continuation did not appear to be the primary problem in our cohort, with only 15% of neurological medication problems related to the duration of treatment. This is one of the first studies to explore *all* issues related to medication in the postdischarge period, and this may be why a greater range of issues were found.

The rise in opiate prescription is troublesome given concerns that the international opioid addiction epidemic is, in part, fueled by iatrogenic provision and easy access to opiates (17, 18). This postdischarge excess may mirror the in-ICU challenge clinicians

face; they are caught between a desire to relieve symptoms and available tools that may worsen longer-term outcomes (19, 20).

Strengths of this study include its multicenter involvement and its systematic approach to analysis; however, there are limitations. We did not control other services which patients attended, and patients may have already had pharmacy reviews—that is, we have documented problems found *after* usual care. As such, we may have undermeasured problems among participating patients, and generalizing from these patients to other populations should be done with caution. In addition, a small number of patients self-referred to the program; this may have impacted the results reported.

In summary, this study demonstrated that over 60% of ICU patients have problems with medicines in the post–hospital discharge period, with a large proportion of these problems being related to psychiatric and pain medications.

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Pamela MacTavish, M.Sc.*
Glasgow Royal Infirmary
Glasgow, United Kingdom

Tara Quasim, M.D., M.P.H., M.B. Ch.B.*
Glasgow Royal Infirmary
Glasgow, United Kingdom
and
University of Glasgow
Glasgow, United Kingdom

Colin Purdie, B.Sc.
University of Glasgow
Glasgow, United Kingdom

Morna Ball, M.Sc.
Glasgow Royal Infirmary
Glasgow, United Kingdom

Lesley Barker, M.Pharm.
University Hospital Crosshouse
Kilmarnock, United Kingdom

Sarah Connelly, M.Pharm., M.Sc.
University Hospital Monklands
Airdrie, United Kingdom

Helen Devine, M.Sc.
Glasgow Royal Infirmary
Glasgow, United Kingdom

Philip Henderson, M.B. Ch.B.
University of Glasgow
Glasgow, United Kingdom

Lucy A. Hogg, M.B. Ch.B.
Victoria Hospital
Kirkcaldy, United Kingdom

Rakesh Kishore, B.Sc.
Glasgow Royal Infirmary
Glasgow, United Kingdom

Phil Lucie, M.B. Ch.B.
Jennifer Murphy, M.Sc.
University Hospital Wishaw
Wishaw, United Kingdom

Peter O'Brien, M.B. Ch.B., B.Sc. (Hons.)
University Hospital Crosshouse
Kilmarnock, United Kingdom

Martin Shaw, Ph.D., M.Sci.
University of Glasgow
Glasgow, United Kingdom
and
National Health Service Greater Glasgow and Clyde
Glasgow, United Kingdom

Laura Strachan, M.B. Ch.B.
Queen Elizabeth University Hospital
Glasgow, United Kingdom

Alan Timmins, M.Sc.
Victoria Hospital
Kirkcaldy, United Kingdom

Theodore J. Iwashyna, M.D., Ph.D.§
Veterans Affairs Ann Arbor Health System
Ann Arbor, Michigan
and
University of Michigan
Ann Arbor, Michigan

Joanne McPeake, Ph.D., M.Sc., B.N. (Hons.)‡
Glasgow Royal Infirmary
Glasgow, United Kingdom
and
University of Glasgow
Glasgow, United Kingdom

ORCID ID: 0000-0001-8206-6801 (J.M.).

*These authors are joint first authors.
‡Corresponding author (e-mail: joanne.mcpeake@glasgow.ac.uk).
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Feasibility and Reliability of Home-based Spirometry Telemonitoring in Allogeneic Hematopoietic Cell Transplant Recipients

Morbidity and mortality from bronchiolitis obliterans syndrome (BOS) remain unacceptably high after allogeneic hematopoietic cell transplantation (A-HCT) (1). Prompt diagnosis may improve outcomes (2). Adherence to home-based spirometry (HS) in lung allograft recipients is high, supporting the feasibility of BOS surveillance (3–6). Low adherence to HS has been a barrier to implementation after A-HCT (7–10), possibly because of psychosocial burnout and fatigue (11, 12). The goal of this pilot study was to *1*) determine the feasibility and validity of HS real-time telemonitoring in A-HCT recipients, *2*) determine factors associated with adherence to HS, and *3*) determine the variability of HS among participants without acute illness.

Methods

We consented and enrolled adult A-HCT recipients at around 100 days post-transplantation between October 2016 and June 2018 at a single transplant center, excluding those who had pneumonia within 4 weeks of screening. The MD Anderson Institutional

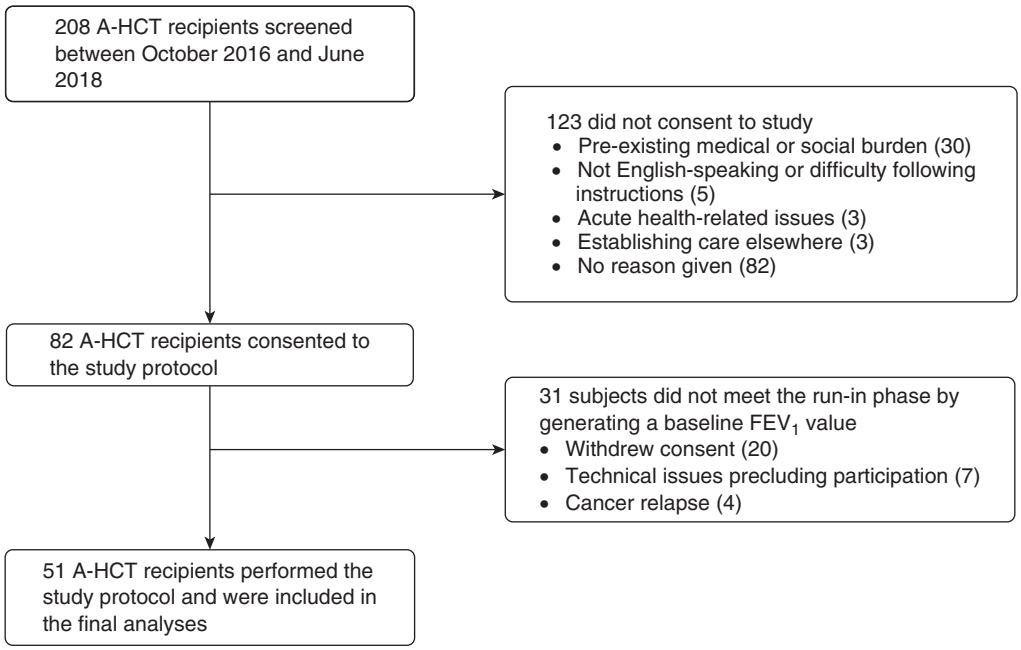

Figure 1. Enrollment flowchart. A-HCT = allogeneic hematopoietic cell transplantation; FEV_1 = forced expiratory volume in 1 second.

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