



A study of the prescribing and administration of immuno-suppressant medication in patients receiving liver, kidney and pancreas transplantation

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Abstract

Introduction

There is little data on immuno-suppressant administration and prescribing to transplant patients. It was considered a high risk area because errors in prescribing and administration of immuno-suppressants can potentially have serious consequences like graft loss, side effects and even death. The reality was however that the lack of data meant that no one knew whether this was an area for improvement or not. The need for data collection was recognised and the aim of this study was to develop and validate a tool to inform the analysis of the patient journey (Failure Mode Effect Analysis) and identify opportunities for quality improvement of immunosuppressant medication use. (Time did not allow for the FMEA to be conducted).

Methods

One-to-one semi structured interviews were conducted with clinical staff (2 pharmacists, 2 nurses and 6 doctors) to explore their perceptions of high risk areas. A case study was done to define the patient journey and identify potential areas where the patient might be at risk of harm. Analysis of database of incident reports (from 2010) was conducted. Lastly, analysis of pharmaceutical care issues identified by clinical pharmacists (2 pharmacists) was done.

Results

Some of the areas identified by staff from interviews were; need for consistent education to patient by all healthcare professions, need for education of staff, communication with primary healthcare professions with regard to risk associated with immuno-suppressants, teamwork amongst the staff on the ward and documentation of interventions. A patient journey detailed where and when high risk processes could occur. The patient journey identified the following areas as high risk: nurses being busy, interrupted or not giving appropriate education. Patients being non-compliant in medications and follow-up meetings, doctors not having clear handwriting, doctors not writing the formulation of immuno-suppressant etc. Database analysis confirmed that Datix® was not a well used reporting system and incidents were mainly in the immuno-suppressant administration category. The incidents reported emphasised the need to follow safe use of medicines policy. Pharmaceutical care issues were not well documented and there were no consistent interventions to confirm particular high risk areas.

Discussion

The richest data came from interviews and highlighted actions that could be used to reduce risk of harm from immuno-suppressive drug therapy. The data collected can be used to generate an FMEA for agreement and use by a multidisciplinary team.

Abbreviations

NHS	-	National Health Service
SPSP	-	Scottish Patient Safety Programme
QIS	-	Quality Improvement Scotland
IHI	-	Institute for Healthcare Improvement
ISMP	-	Institute for Safe Medication Practice
QIT	-	Quality Improvement Team
TI	-	Therapeutic Index
RIE	-	Royal Infirmary of Edinburgh
POD	-	Patients Own Drugs
FMEA	-	Failure Mode Effect Analysis
PDSA	-	Plan-Do-Study-Act
RPN	-	Risk Priority Number
HDU	-	High Dependency Unit
ITU	-	Intensive Treatment Unit
GP	-	General Practitioner
CNI	-	Calcineurin Inhibitor
AZA	-	Azathioprine
SLTU	-	Scottish Liver Transplant Unit
BNF	-	British National Formulary
MMF	-	Mycophenolate mofetil

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1 Introduction

1.1 Background

National Health Services (NHS) Lothian is part of NHS Scotland. Health service is distributed in the country through fourteen regional NHS boards[1] where NHS Lothian is one of these fourteen. NHS Lothian is an important employer and has almost 28 000 staff which includes 15 000 nursing and midwifery staff and 2700 medical staff. NHS Lothian cares for a population of 800 000[2] locally but they also offer some specialist services to the rest of the country. Among some of the specialist services they provide are the kidney and liver and pancreas transplantations.

Quality improvement and patient safety are both important focus points of NHS Scotland and this master thesis is part of the work to improve patient safety and minimise harm to patients, in this case; patients receiving solid organ transplantation.

There are many definitions of harm.

The British Medical Association supports the definition of harm as:

“Adverse outcomes or injuries stemming from the provision of healthcare” [3]

Another definition of the prevention of harm is:

“Freedom from accidental or preventable injuries produced by medical care.”[4]

The Scottish patient safety programme[5] (SPSP) aims to make the healthcare system reliable and safe. SPSP’s objective is to improve the safety of hospital care across the country. SPSP is co-ordinated by [6]NHS Quality Improvement Scotland (NHS QIS) which seeks to improve the quality of patient care throughout the country.

SPSP states that [5]UK and international evidence indicates that 1 in 10 patients experience an adverse event in hospital where adverse events are defined as *unintended consequences of care* like for example a drug error. Research shows that 50% of adverse events can be avoided if rigorous patient safety processes are routinely followed. Adverse events can result in severe emotional, psychological and physical impact on patients, but the costs are also significant. Adverse events are estimated to cost NHS Scotland around £200 million each year in extra treatment and lost bed days.[7] The National Patient Safety Agency calculated that preventable medication errors cost the NHS more than £750 million each year in England. [8] This is money that could benefit countless patients and staff and optimise patient care if there was a way to minimise the costs associated with medication.

Institute for Healthcare Improvement (IHI)[9] is an American based non-profit organisation. They work with health carers all over the world to test new models and motivate for change so that the best practice can be found and adopted by everyone. The IHI believe that everyone deserves safe and effective health care. The essence of the thinking is to share knowledge, collaborate and improve health and health care everywhere for everyone. In order to accomplish that, innovative ideas are the key to success.

IHI defines adverse drug events as:

“Harm to the patient from medications, whether or not the result of an error.”

Conventional efforts to detect adverse events have focused on voluntary reporting and trying to investigate errors that do happen. According to IHI, public health researchers have established that only 10 to 20 percent of errors are ever reported and, of those, 90 to 95 % cause no harm to patients [10]. The remaining ones can be the cause of significant harm and high costs however. There is a need for a system that not only detects errors and allows for

staff to report without it taking up too much of their time, but also encourages no-blame reporting so that staff are not afraid to report errors they have made themselves. There needs to be an emphasis on how important it is to report errors in order to be able to investigate them and make changes to minimise them. There is no current system in place in NHS Scotland that will let people detect and report errors within a time limit without resulting in blame.

Williams[11] defines medication errors as:

“Any error in the prescribing, dispensing, or administration of a drug, irrespective of whether such errors lead to adverse consequences or not”

He states that medication errors are the single most preventable cause of harm to patients.

The article also emphasises the causes of medication errors, one of them being that medical staff responsible for most of the prescribing in hospitals can be relatively inexperienced and so mistakes are more likely to happen. Electronic prescribing can be a solution to eliminate the risks of prescribing errors. It also has its weaknesses however; although some sources of errors are eliminated, others are encountered.

1.2 Why transplant was chosen as a project topic

The transplant ward was chosen as a project topic because immuno-suppressants were considered high risk medicines and errors in administration and prescribing of these medicines could result in serious consequences. Some of the consequences include graft rejection or toxicities such as nephrotoxicity, hepatotoxicity, disturbances in glucose metabolism (can lead to diabetes), neurotoxicity, malignancies, increased risk of infection and gastrointestinal disturbances in terms of nausea, vomiting and diarrhoea which again can alter uptake of drugs from intestine. The quality improvement (QIT) team of the transplant ward

recognised immuno-suppressant medications as high risk and suggested the area of interest to the lead pharmacist at RIE and the senior pharmacist at the liver transplant ward at the RIE.

The NHS patient safety website defines high risk medication as:

“High risk medicines are medicines that are most likely to cause significant harm to the patient, even when used as intended. The Institute for Safe Medication Practices (ISMP) reports that incident rates with this group of medicines may not necessarily be higher than with other medicines, but when incidents occur the impact on the patient can be significant.”[12]

Typically examples of drugs considered high risk medications are anticoagulants (i.e. warfarin and heparin) opiates and insulin[13]. Immuno-suppressants do however fit under the definition in the aspect that they can cause significant harm even when used as intended. There are a lot of individual patient factors that determine this. Immunosuppressant therapy in transplant patients is a complex matter as many of the drugs may result in severe side effects. Many of these drugs are also subject to drug interactions.

Although there are many potential error sources and serious consequences if immuno-suppressants are prescribed or administered wrongly, there is very little data and few studies that have actually been carried out on this particular topic in this context. Therefore the QIT and pharmacists at the RIE along with the investigator recognised the need for data collection and investigation to establish whether this is a topic that needs further attention or not.

1.3 Datix®

Datix[14] is a software programme that aims to help healthcare workers increase patient safety and reduce harm to patients. Today more than 70 % of the UK NHS use Datix. Datix is a safety improvement tool [14] intended to improve patient safety. Staff can voluntarily report incidents on Datix. The reporter describes the situation and fills out a form that allows details of the situation to be given and explained. The incident is investigated by the appropriate person i.e. the charge nurse or section head who allocates the grade of severity (low, medium or high). However, it is a known weakness of Datix that it is not used consistently in hospitals as Datix relies on staff to report all incidents in order to be a reliable tool for investigating trends. Voluntary reporting and lack of time and incentive to report means that incidents are rarely recorded on Datix which makes the few reports that do come in, impossible to generalise or conclude anything from. One of the problems may be the fear of blame between staff. Datix reporting is often associated with blame instead of focusing on lesson learned from the reports. It is important to focus on medication error reporting as no-blame processes that are important to improve patient safety and minimise harm to patients.

A project carried out by pre-registration pharmacist trainees in NHS Lothian in 2008 found that[15]:

“Over the total observation period (7 weeks) 3 incidents were documented on the hospital reporting system and 261 medication related incidents were observed by the investigators in the seven specialties.”

A system should ideally allow people to easily report incidents in a reasonable amount of time, learn from them and be able to discuss improvements without feeling a sense of guilt or blame. There is clearly a lack of such a system. In order for an incident reporting system to be

successful, the people using it need to learn from the mistakes and also be motivated to see the importance of this. Staff need to be provided with sufficient education and guidance as to what types of incidents or near-misses should be reported and how to best describe it so others can learn and benefit from it.

A study[16] done in north east of Scotland on Datix incident reports showed that over a 46 month period 80 % of reports were made by nursing and midwifery staff. The medical and dental profession reported the lowest number of incidents. This is an indication that Datix reports regard for the most part administration errors as nurses will pick these up. Though it can be argued that it is not only doctors who can detect prescribing errors, the errors that happen in prescribing might never be reported by doctors and so are largely unknown. The study also states that;

”Approximately 20 % of deaths from adverse events are related to medication incidents, costing the NHS an additional £500 million annually. Less than 5% of adverse events are reported.” [16]

Quality improvement and patient safety projects rely on there being data to show the status quo and what is actually going wrong in order to improve upon this. This is however very difficult when most incidents remain unreported. The result being that one can only approximate if and how many errors are occurring, but there are no actual numbers for it. Medication errors might be prevented if the right measures and processes were put in place and followed.

1.4 One-stop dispensing and self administration

1.4.1 One-stop dispensing

One-stop dispensing[17], also known as ‘dispensing for discharge’ essentially means to combine in-patient and discharge dispensing into one single process. Along with the use of patients own drugs (POD) this results in quicker discharge by reducing dispensing time, reduced drug errors and reduced wastage and hence costs. The use of POD may contribute to more accurate drug history as patients are familiar with the packs and can easier identify drugs and doses.

1.4.2 Self administration

Specific for the transplant ward is self administration which is a three stage process whereby a transplant patient is ultimately allowed to administer his or her own medicines after a nurse or pharmacist has assessed them, provided authorisation and the patient has satisfied a number of compliance checks. Patients are also encouraged to bring their medication with them when they are admitted to hospital and so they can keep taking their own drugs as well. This is called use of patients own drugs (POD). Use of POD contributes to the overall aim of letting more patients self administer their own drugs. Patients will receive education beforehand from clinical staff about self administration and their drugs and are given the chance to ask any questions that might come up.

The self administration forms are filled out by nurses or pharmacists includes questions concerning whether the patients has received education, is on intravenous drugs, is confused, has had a previous overdose, can open bottles etc. The medications the patient uses are placed in a locker beside their bed, and the nurses have the key to it. The patients normally start on stage three during self administration. During stage two the nurse has the key to the locker,

opens the locker, allows the patient to take their medications and do daily checks of the content of the locker. At stage one the patients have the key to their locker and the nurses do weekly compliance checks. The self administration in the transplant ward applies mostly to oral drugs.

The patients receive a medication reminder book known as ‘the green book’ before they are discharged from hospital. This book contains a list of all the patient’s medications, and a few notes on how to take them. It should ideally be updated every time there is a dose change to any medications. Patients are encouraged to bring the green book to every clinic visit.

Self administration in the transplant unit is aimed at preparing patients for going home and giving them the opportunity to get any questions answered whilst still in the hospital setting. The patient is meant to feel more confident when going home and should know all they need to know about medications, dosages and side effects. In transplant patients this is an important issue especially for liver transplant patients where many of them have not been on many medicines at all pre-transplant, whereas post-transplant they will leave with several different medications that are all vital to the success of their graft survival. Going home and remembering everything might prove to be a bigger challenge than patients first imagine it to be whilst in the hospital setting. Drug compliance is such an important part of a transplanted patients’ health and that is emphasised throughout a transplant patient’s journey.

1.5 Liver, kidney and pancreas transplantation

Success rates for organ transplantation the last few years have improved remarkably and organ transplantation now saves many lives. For kidney transplant patients who no longer need dialysis, it makes life easier and increases quality of life.

1.5.1 Liver transplantation

Liver transplantation [18] success rates have increased the past years but there is no equivalent increase in cadaveric donors (i.e. organ from an organ donor who has died resulting in brain stem death) and so the number of patients on waiting list keeps increasing and some patients die whilst waiting for an organ. The main problem remaining is the shortage of cadaveric donors. One of the solutions to this has been living donor transplantations where often a relative donates part of his or her liver to the recipient. Liver transplantations are matched based on size of organ and blood group. However not all people have someone willing to donate part of their liver or fill the criteria for living donor transplantation and living donor transplantations remain uncommon at the RIE. Shortage of cadaveric donors is still the major issue with liver transplantations.

1.5.2 Kidney transplantation

Kidney transplant has changed the life and future of patients with kidney failure. Before, dialysis was the only option but now a kidney transplant can restore health. The kidney can come from a cadaveric donor or a close relative if it is a living donor transplantation. As for any organ transplant, there is also here a shortage of organs. Kidneys are allocated by blood and tissue type.

1.5.3 Pancreas transplantation

Pancreas transplantations are not as common as liver and kidney transplant. It is often an option for patients that have diabetes and renal failure and need a kidney and pancreas transplantation at the same time. Pancreas transplantation is only suitable for type 1-diabetes is allocated by blood group.

1.6 Immunosuppressant medication

1.6.1 Background

The immune system is the body's natural defence. Transplanted cells from a donated organ or graft are considered foreign and unfamiliar and so the body's immune system will seek to destroy them. Therefore immuno-suppressants are needed to prevent the body from rejecting the new organ. After transplantation, they have to be taken every day for the rest of the patients' life. Immunosuppressant medications[19] are hence at the core of an successful organ transplantation. If blood levels of immuno-suppressants are too high, side effects and infections can occur. If levels are too low, organ rejection may occur. Optimal dosing and combination of immuno-suppressants is key and it needs to be finely tuned. Some of the immuno-suppressants have a narrow therapeutic index and show significant variability in blood concentrations between individuals. Therefore blood monitoring of some of the immuno-suppressants (tacrolimus and ciclosporin) plays a big part of the adjustment of the dosage regimen. Immuno-suppressants can cause serious side effects even at the right doses which is why it is important that patients understand how vital it is for them to be compliant if they do experience side effects.

During the first few months after organ transplantation risk of rejection is at its highest and hence so are the doses of the immuno-suppressants. To avoid unnecessary high doses of immuno-suppressants and hence side effects, a dosage regimen of several different immuno-suppressants are used. This lowers risk of serious side effects instead of using one single immuno-suppressant at a very high dose, several with different modes of action are used at lower doses. The risk of infection is also at this point highest as the high doses of immuno-suppressant medications lower the ability of the immune system to fight of infections. The patients are monitored very closely for signs of infection.

All immuno-suppressant medication used in transplant can be considered high risk medication. Transplant patients are a complex group of patients that have a range of different co-morbidities and patients can be of all ages. Also, graft rejection is dependent on many factors including immune response which is very individual. This makes drug therapy and development of standard protocols for therapy a complex issue. Nonetheless this group of patients need to be especially compliant as non-compliance can potentially lead to organ rejection, severe side effects and even death.

1.6.2 Antiproliferative immuno-suppressants

Azathioprine (AZA) is widely used for transplant recipients. It is metabolized to 6-mercaptopurine which is further converted to active 6-thioguanine nucleotides. These metabolites are incorporated into DNA where they inhibit purine nucleotide synthesis. Blood tests and monitoring for signs of bone marrow suppression are essential in long-term treatment with AZA. Two serious side effects are bone marrow suppression and hepatotoxicity. The side effects are dose dependent.

Mycophenolate mofetil (MMF) is metabolised to mycophenolic acid which has a more selective mode of action than AZA. It inhibits purine synthesis but it is specific to lymphocytes. It is licensed for the prophylaxis of acute organ rejection in renal, hepatic or cardiac transplantation when used in combination with ciclosporin and corticosteroids and is thought to be CNI sparing so a lower dose of CNI's can be used. Common side effects include diarrhoea, bloating, nausea, heartburn and high blood pressure.

For liver transplantation the out-patient guidelines[19] state that MMF and azathioprine are similar drugs but MMF is a more potent immuno-suppressant than azathioprine. MMF is used in three situations at the SLTU[19]:

- 1) “In patients with early chronic rejection, in combination with tacrolimus. In patients with renal impairment to allow either:
- 2) Replacement of CNI with MMF and Prednisolone
- 3) Dose reduction of CNI in combination with MMF”

From the website for Edinburgh Renal Unit (EdRen) [20] all patient receiving kidney and/or pancreas transplantation are given MMF unless they are unable to tolerate it, in which case AZA can be given. If patients are considered low risk recipients then MMF can be replaced with the less potent AZA in the long term immuno-suppression drug regimen.

1.6.3 Calcineurin inhibitors (CNIs)

The CNIs are ciclosporin and tacrolimus and they are considered the cornerstones of immuno-suppressive regimens. They have similar modes of action. They decrease T-cell activation by inhibiting calcineurin resulting in T-cells that are unable to induce an immune response. CNIs can result in kidney damage at particularly high doses. It is thought that the kidney damage in both CNIs has similar mechanisms. One proposed mechanism for this is [21] that ciclosporin causes reversible impairment of glomerular filtration and irreversible fibrosis.

One proposed mechanism [22] for the nephrotoxicity resulting from CNI use is that it is the result of vasoconstriction of intra-renal vessels causing decreased renal blood flow.

Another study [23] done on “Calcineurin inhibitor-induced renal allograft nephrotoxicity” concludes the following:

”Pathophysiologic mechanisms behind CI (calcineurin inhibitors) nephrotoxicity are only partially elucidated (...) the main effect responsible for toxicity still remains unsolved (...) Since CI remain, despite their nephrotoxic effect, the mainstay of immunosuppressive protocols, their use needs to be optimized. The main measure to prevent nephrotoxicity is the

effort to reduce systemic levels and keep local renal exposure to CI and their metabolites as low as possible.” [23]

Other troublesome concerns with both of these drugs are headaches, tremors, hypertension and hyperkalemia [22]. In addition tacrolimus can increase blood sugar and result in diabetes[24]. Ciclosporin can cause high blood pressure, increased hair growth and sore/swollen gums [25].

Tacrolimus is now considered the first line agent for kidney, pancreas and liver transplantation at the RIE. From the liver in-patient protocol[26] for liver transplants at the RIE it is stated:

“Prograf (tacrolimus) is to be prescribed following liver transplantation.”

At the renal unit website, EdRen [20], it is stated under prograf/advagraf (tacrolimus) that it is:

“The lead agent in standard triple therapy for all patients.”

There have been many studies done on tacrolimus versus ciclosporin as the primary immunosuppressant and most show tacrolimus to be superior. One study [27] done on tacrolimus versus ciclosporin in liver transplanted patients showed tacrolimus to be superior in patient survival, graft survival, and preventing acute rejection. However it did also show an increase in post-transplant diabetes. Another study[28] done on the same topic in patients transplanted for kidneys showed improved graft survival and prevention of rejection, but increased post-transplant diabetes and other side effects. The authors conclusion was [28]:

“Tacrolimus is superior to cyclosporin in improving graft survival and preventing acute rejection after kidney transplantation, but increases post-transplant diabetes, neurological and gastrointestinal side effects. Treating 100 recipients with tacrolimus instead of cyclosporin

would avoid 12 suffering acute rejection, two losing their graft but cause an extra five to become insulin-requiring diabetics.” [28]

An important factor about these agents is that they come in a variety of different formulations which are not bioequivalent. It is important for patients and healthcare staff not to confuse these with each other as switching between them should only be done under close monitoring by transplant specialist. Although not as much used at the RIE, ciclosporin comes as Sandimmune, Neoral and generic formulation. The two formulations of tacrolimus most frequently encountered at the RIE are Prograf and Advagraf. Prograf is an immediate release formulation taken twice daily. Advagraf is a prolonged release formulation that is taken once daily. For liver transplantation at RIE as stated above, Prograf is prescribed following transplantation according to the in-patient protocol.

From EdRen.org:

“Prograf will be used in the initial post-operative period. Patients can be switched to Advagraf once stable levels have been achieved, usually in the outpatient clinic.”

1.6.4 Corticosteroids and other immuno-suppressants

The use of corticosteroids is kept to a minimum or eliminated because of the long-term side effects [22]. However, they still remain powerful immuno-suppressants and are frequently used in acute rejection and in preventing rejection. They do however have serious side effects like irritation in the stomach, weight gain, rounded face, thinning of skin and bones (osteoporosis) and hyperglycaemia (diabetes) and so effort has been made to minimise the use.

Basiliximab is a monoclonal antibody that prevents T-lymphocyte proliferation; it is used for prophylaxis of acute rejection in allogenic renal transplantation. It is licensed with ciclosporin and corticosteroid immuno-suppression regimens. At the RIE it is used in combination with

tacrolimus for induction therapy; it is given in two doses, first at the time of transplant and the next dose after four days.

All kidney/pancreas transplanted patients at RIE receive basiliximab. For liver transplanted patients the in-patient protocol[26] chapter 7.2 states the following about basiliximab and when it is used:

“BASILIXIMAB: This interleukin-2 receptor antagonist will be given in elective patients with serum creatinine > 150 micromol/l or eGFR < 40 ml/min.”

In the liver unit, basiliximab is used in patients with renal dysfunction to allow delayed introduction of tacrolimus which is more nephrotoxic than basiliximab.

Sirolimus is a non-calcineurin inhibiting immuno-suppressant only licensed for renal transplantation. It is also used in liver transplanted patients. It inhibits T-cell activation via suppression of proliferation driven by interleukin 2 (IL-2) and interleukin 4 (IL-4). Interleukins are a group of cytokine signalling molecules vital to normal immune response. The main benefit with sirolimus is that it lacks the nephrotoxicity that is an issue for the calcineurin inhibitors.

1.6.5 Drug interactions

Drug interactions are major focus with immuno-suppressants. The most common interactions are between CNI's and other drugs metabolised in the liver via the CYP3A4 enzyme system. Common interactions are listed in the out-patient protocol for liver patients and include interactions of CNI's with erythromycin, fluconazole, clarithromycin and amiodarone. Most of the drugs used in transplant are specialised and not used frequently in other conditions. The GPs take on some of the non-specialist prescribing for the transplant patient in the community setting after transplantation and drug interactions remains a potential problem. The GPs need to work in close contact with the transplant doctors in order to assure that no harm comes to

the patient when new drugs are introduced. Standard drugs used even for minor illnesses can potentially interact with many of the immuno-suppressants, and the GPs need to be informed about this in order to avoid drug interactions. The GPs get a copy of the discharge letter and can access shared care protocols. The GPs also get clinic letters after each clinic visit. This includes a list of medications.

1.7 Principles of the Failure Modes Effect Analysis (FMEA)[29]

The FMEA is a tool to evaluate a process that can be used in a variety of different settings. It helps identify where the weaknesses (failure points) are, assess these weaknesses and get ideas for improvement so the process is less likely to fail. FMEA is a method adopted by the SPSP to assess a process. As it is a fairly new method of improving quality, there is little data on the exact long term benefits of doing an FMEA. A PhD done by Nada Ates Shebl[30] in 2010 confronted the issue of promoting patient safety using the FMEA. The author's conclusion was that the FMEA was:

“...FMEA is a useful tool to aid multidisciplinary groups in mapping and understanding a process of care. However, it is not a valid or reliable tool for identifying the failures that can occur or scoring the severity, probability and detectability. Healthcare organisations should not solely depend on their FMEA results to ensure patient safety.” [30]

The author did state that the FMEA was subjective and depended upon the specific multidisciplinary team involved, which are known weaknesses of this method.

Another study [31] published by the British Journal of Clinical Pharmacy in 2009 used the FMEA as a tool to improve patient safety of rituximab use in anti cancer therapy. The conclusion was:

”FMEA was found to be an effective tool for identifying potential areas of risk in the use of rituximab, and the methodology could be applied to other high risk medicines.”[31]

In this project, the FMEA is thought to be part of the overall data collection and is not meant to be the only method relied on.

The steps in the process of an FMEA are:

- 1) Select a process to evaluate with FMEA this is usually a high risk process
- 2) Recruit a multidisciplinary team
- 3) Have the team meet together to list all of the steps in the process
- 4) Have the team list failure modes and causes
- 5) For each failure mode, have the team assign a numeric value (known as the Risk Priority Number, or RPN) for likelihood of occurrence, likelihood of detection, and severity
- 6) Evaluate the results
- 7) Use RPNs to plan improvement efforts

The FMEA was chosen as a method for evaluating the process of prescribing and administering of immuno-suppressants, considered to be high risk medications. Traditionally high risk medications are the ones considered in chapter 1.2, but in this project immuno-suppressants were considered high risk medications. Although they are not traditionally thought of in this context, they do fit under the definition in chapter 1.2.

The FMEA focuses on the process and on *what* could go wrong instead of focusing on *who* may allow for something to go wrong. In that way the no-blame aspect is at the centre of attention. By doing an FMEA one can put measures in place to prevent failures from happening and reaching the patients. An FMEA can therefore be a good way to improve patient safety.

However, there are weaknesses to the FMEA approach. The most important weakness being as mentioned above, that the FMEA is a subjective way of risk assessing. The process is scored in terms of risk assessment by numeric values set by the different people involved in the FMEA team. The scores of high risk areas are therefore very subjective and rely on each individual in the group coming to a consensus. This is why it is useful to have a multidisciplinary team, so different grades of all types of staff involved, are included. This will make the final scores based on a broad variety of opinions of staff and in that way give a well rounded view of the process and help identify all areas of risk in the process. Different views from different professions on the same process are taken into account by using a multidisciplinary team.

The FMEA's strength lay in carefully identifying which people to include and getting them to think thoroughly through the process before scoring each step. It also relies on that the fact that the members of staff selected are motivated for change and not afraid to identify weaknesses in the process.

1.8 Potential high risk areas in administration and prescribing of immuno-suppressants

Prescribing on the transplant ward at the RIE is done for the most part by middle grade doctors however it is done under close supervision of senior doctors. Electronic prescribing is not in place at the RIE so there is much relying on clear hand writing, giving written information and comments on kardex in an understandable way. Nurses rely on prescriptions to be clear in order for misunderstandings and errors to be avoided.

Medicines administration can be considered a potential high risk area. Nurses are understaffed at times and they have little time to complete tasks. A lot of people rely on nurses and they have many responsibilities on the ward. There are always people asking questions whether it be relatives of patients or other staff and this can be a source of distraction and ultimately lead to errors. Nurses getting distracted from what they were initially doing can lead to patients not receiving medications at the right time. Administering patient's medicines takes a lot of concentration to rule out any potential mistakes. Nurses are trained and should follow the NHS Lothian Safe Use of Medicines Policy and Procedures[32]. Interruptions often cause lapse in concentration which can lead to errors and processes have been put in place to minimise these interruption such as the tabards that the transplant wards have now introduced. The nurses now wear red vests called tabards which say; *Do not disturb. Nurse on drug round.* This is a measure put in place to minimise chances of nurses making mistakes whilst on drug rounds.

1.9 The model for improvement

The model for improvement is a tool adopted by SPSP that can be used to help evaluate a process and identify areas for improvement. The model for improvement[33] is a tool intended to accelerate improvement. It consists of two parts. The first part is answering the three important questions.

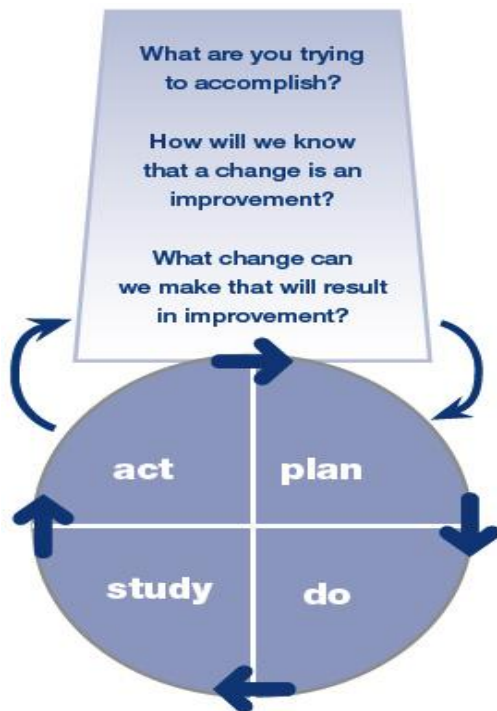


Figure 1: Model for improvement and PDSA cycle[34]

Answering these questions allows the people involved to set aims for what they're doing, set up specific measures to see if the change is leading to improvement, and recognising the changes that are likely to lead to improvement.

The second part is the Plan-Do-Study-Act cycle (PDSA). This is a test to check a change by planning it, trying it, observing the results and acting on what is learned from it all. This project is considered the planning part of the PDSA-cycle. The rest of the cycle can be if the recommendations for improvements resulting from this project are implemented (do), then to see whether this made a difference (study) and lastly act on the results from the study (act).

2 Aims and objectives

2.1 Aim

Develop and validate a tool to inform the analysis of the patient journey (Failure Mode Effect Analysis) and identify opportunities for quality improvement of immunosuppressant medication use.

2.2 Objectives

1. Map the patient journey before and after transplantation and identify points which present risk of harm due to potential adverse events associated with immunosuppressant medication use.
2. Characterise the harm assessment based on historical incident reports and recorded interventions. Expand the harm assessment using perceptions of clinical staff.
3. Further characterise the assessment using data from prospective survey(s).
4. Validate the FMEA tool by presentation of findings to an expert group.

2.3 Subjects and settings

2.3.1 Study design

The study included semi-structured one to one interviews, database analysis of Datix incident reports, case note review and retrospective review of care issues documented by pharmacists.

2.3.2 Subjects and settings

The project team comprised the investigator Kinjal Patel, Moira Kinnear Head of Pharmacy Education, Research and Development and Lecturer in Clinical Practice, Katherine Davison the clinical pharmacist from the liver transplant ward, Scott Garden the lead pharmacist and

lastly Sara Dyrhaug fellow investigator. The parallel project carried out by Sara Dyrhaug was on the drug Valganciclovir used in transplant patients for prophylaxis and treatment in Cytomegalovirus disease.

The project included wards 206 (transplant ward) and 117 (high dependency unit, HDU) at the Royal Infirmary of Edinburgh (RIE). All liver and simultaneous kidney and pancreas transplanted patients are in ITU (118) immediately after transplant operation and with no complications they are usually transferred to HDU after 24 hours. Kidney transplanted patients go to HDU post-operative. All patients are then transferred to the ward area (206) when their condition improves. If the patient is readmitted they might be admitted to other wards initially or to other hospitals if the transplant hospital is far away. Often they do however end up on the transplant ward no matter what their illness is because they are a specialised group of patients.

The teams on the wards are multidisciplinary and consist of nine consultant surgeons, six consultant hepatologists and ten consultant nephrologists. Also in the wards are nurses, various grades of medical staff, transplant co-ordinators, a dietician, two pharmacists, a social worker, physiotherapists and psychiatrists who all work together to optimise patient care. Each week the team (there is one renal team and one liver team) that looks after the ward consist of a junior grade doctor, medical registrar, surgical registrar, consultant physician and consultant surgeon. There is one registrar attached to each team of the liver and kidney teams; one hepatologist registrar, one nephrologist registrar and one surgical registrar. The registrars rotate approximately every two months. One junior doctor is attached to each team and they rotate 4 weekly.

The doctors were classified as junior grade (Foundation Year one and Foundation Year two, Senior House Officer), middle grade (speciality registrars) and senior grade (consultants).

Patient criteria for review of pharmaceutical care issue documentation:

1. In-patients only
2. Post-transplant only. Including patients readmitted for complications of any sort.
3. Transplant patients must be on one of more of the following immunosuppressant medications: Tacrolimus, Ciclosporin, Prednisolone, Mycophenolate mofetil, Azathioprine, Sirolimus or Basiliximab

Clinical staff criteria for participation in interviews:

1. Included staff of different grades (senior and junior)
2. Included staff with different duration of experience from the transplant wards
3. Include nurses and doctors in interviews and multidisciplinary team
4. Include the pharmacists from the transplant ward for interviews

The doctors and nurses included in interviews consisted of a convenience sample of people who were available at the time allocated to the investigator.

2.3.3 Ethics approval

The transplant QIT suggested the area of interest to the liver transplant ward pharmacist and recognised the current lack of data around the project topic.

The project involved no personal identifiable information about patients and staff. A copy of the protocol was sent to Alex Bailey (Scientific Officer, South East Scotland Research Ethics

Service). Based on that, the project was classified as service evaluation and did not need NHS research ethical review. Full letter attached in appendix 2.

3 Methods

3.1 Patient journey

The investigator undertook a case study to illustrate the patient journey before and after transplantation to identify potential and actual drug related problems in immuno-suppressant drug therapy. Self administration and nurse administration were looked into as a potential risk where things can go wrong. One of the liver transplant patients admitted in the fall of 2010 was selected by the transplant ward pharmacist. The investigator reviewed the clinical case notes and medicines charts and documented the patient journey in terms of chronological clinical management. No identifiable personal data was included (names, detailed history, personal information, full date of birth etc). To get a clear picture of what the patients' issues were and how staff dealt with it, the investigator attended ward rounds and multidisciplinary ward meetings where issues that had been encountered throughout the week were addressed and patients were discussed. Through this the interaction and collaboration between different health professions and the multidisciplinary teamwork became evident. In addition the investigator attended clinic visits to be able to get a clear picture of patients' issues regarding immuno-suppressants both before and after transplant. Also the clinic visits and ward meetings allowed the investigator to help map the process of the patient journey and see issues from both medical staff, nurses', pharmacists' and patients' point of view. To fill in any blanks, the investigator used in-patient and out-patient policies and protocols for the liver transplant ward, including information documentation. These contained detailed descriptions

of guidelines [19, 26] regarding the immuno-suppressant and issues related to them such as interactions, side effects, the GPs role, monitoring etc.

3.2 Characterising the harm assessment

3.2.1 Historical incident reports; Datix

Harm was characterised by using historical Datix incident reports to identify which type of drug related problems were associated with immunosuppressant drug therapy, recognising the underreporting in the use of Datix. The investigator emailed the person responsible for Datix reports on the transplant ward (206+117) and hardcopies of reports from 2010 were provided for analysis. The data for immuno-suppressants was extracted from all reports from this area. In addition the investigator and a fellow investigator observed when one of the pharmacists at the RIE completed a report. The pharmacist went through the process of filling out the reports and explained the steps.

3.2.2 Staff perceptions; interviews

Staff on the transplant ward were made aware of the project (and a parallel project) through presentation of the protocol(s) at a transplant ward meeting (appendix). Staff had an opportunity to express opinions and ideas about the project(s). The liver transplant ward pharmacist had sought approval from the transplant QIT whose comments were also included in the project design.

A questionnaire was designed (appendix) for one-to-one structured interviews with a range of doctors and nurses from the transplant ward to gather their opinions about risks in the process of prescribing and administering of immuno-suppressant agents in patients having undergone

solid organ transplantation. The interview schedule took into consideration data gathered from Datix reports and the patient journey (case study) and was reviewed by the project team.

The questions for the questionnaire were first drafted by the investigator and input from the transplant pharmacist and academic supervisor was then given. The questions asked were focused around where in the process of prescribing and administering of immuno-suppressants, things were likely to go wrong. The administration part focused on nurse administration and self administration with focus on patient education and knowledge about their immuno-suppressants. Lastly in the administration part, a few questions were included regarding patient adherence to drug regimen (compliance) and how staff perceived this. It also focused on the GPs role in a transplant patients' drug therapy and how GPs were involved in a transplant patients' use of immuno-suppressants. This was to see whether the GPs involvement could be a potential high risk area for example in the case of drug interactions as a potential issue. The same questions were asked to all staff including junior to senior grade nurses and doctors from both renal and liver transplant wards except question two regarding prescribing:

Question 2: Monitoring is important in the use of immuno-suppressants, and blood tests are taken frequently. How are the results of the blood tests taken into consideration at the time of prescribing?

This was left out for nurses as it regarded the specifics of monitoring and prescribing and was not considered within their area of expertise to answer. Staff were invited to participate via the transplant ward liver pharmacist and follow up communication (appendix) to arrange an interview time and place was undertaken by the investigator who attached a copy of the protocol for information. A convenience sample of a range of staff were selected; four doctors and one nurse. All replied and would participate except for one doctor who never replied. The

charge nurse then provided the investigator with two nurses willing to participate in interviews; one junior and one senior grade nurse. The doctors that replied were booked in for interviews and the investigator met with them in their offices. The renal transplant pharmacist organised two more doctors for interviews; one junior and one middle grade doctor. The liver transplant ward pharmacist arranged for one additional junior doctor to be included. All the interviews were recorded and all staff participating were made aware of this at the start of each interview. They were also informed that the tapes would remain anonymous and would be destroyed following transcription. The recordings were transcribed.

The pharmacists on the transplant ward were also asked to list the care issues they encounter most frequently (appendix 7).

3.3 Prospective surveys; pharmacist check-list

The intention was to further characterise the assessment by using data from prospective surveys. The investigator adapted a checklist based on the categorising of common causes of drug therapy problems done by a previous master student[35]. The adaption was made by the investigator and transplant pharmacist by carefully selecting which points to include in the checklist based on relevance to the topic of this study. The check list was also made as user friendly as possible to encourage completion. This would also rule out potential mistakes that could be encountered based on too much text and the check list being too complex. The two pharmacists on the transplant ward were to tick the appropriate boxes in the checklist. The checklist was used over a time scale of two and a half months.

3.4 FMEA

Although the intention was to collate all the information retrieved from other data collection and conduct an FMEA to be able to agree the processes and score the levels of risk at each stage in the process, time did not allow this part of the study to be undertaken.

4 Results

4.1 Patient journey

The case study (appendix 9) allowed the investigator to map the process of a transplant patient's journey. The staff involved at each step and communication between staff and with the patient was also clarified. The process regarding self administration and patient education were highlighted. See patient journey in appendix for more details.

4.2 Data collection

4.2.1 Datix®

When reports are written on Datix the staff who report, put in their ID and location. The Datix incident form that staff fill out is quite extensive and what has to be filled out depends on what the reporter actually fills in as they go along. In the printed report the following columns come up; *ID, Location, description, action taken, lesson learned, drug name, grade and opened date*. This is only part of what the reporter fills out however. A hypothetical example of what a report looks like when printed out is given below.

Table 1: Hypothetical example of a Datix report

ID	Location (exact)	Description	Action taken (investigation)	Lesson learned	Drug name	Grade	Opened date
123 456	Ward 206 Transplant	Prograf given instead of Advagraf	Consultant contacted	Need for staff training recognised	Tacrolimus	Medium	01.01.2011

Table 2: Datix reports from the transplant ward

Total number of reports ward 206 (transplant) for 2010	34
Number of reports lacking specifications for specific drug in the column <i>drug name</i> *	8
Number of reports regarding immuno-suppressants**	9
Number of reports regarding medication schemes in general***	5
Number of reports on immuno-suppressant regarding missed doses	5
Number of reports regarding immuno-suppressants graded as low	6
Number of reports regarding immuno-suppressants or medication schemes in general graded as medium	4
Number of reports regarding tacrolimus	6
Number of reports not regarding immuno-suppressants or medication schemes	20

*Not all reports are regarding immuno-suppressants. One report has *tacrolimus* in the *description* column and is regarded as a report on immuno-suppressant.

**Including only those reports with specific names of immuno-suppressants. Some reports did not include any drug names.

*** These did not have any specific immuno-suppressant drugs mentioned

The reports were dealt with in terms of reports containing specific medication names, reports not concerning medications (one report was as an example regarding fluid charts) and reports regarding medication schemes in general where the staff filling out the report often put *multiple* in the drug name column. There were eight reports on immuno-suppressants where the drug name was mentioned in the *drug name* column. In addition there was one report

missing drug name but that had tacrolimus written in the description column. This was then regarded as one of the reports on immuno-suppressants. The reports regarding medication schemes in general often concerned all or some of the drugs the patient was on, multiple medication doses missed, multiple medication errors in kardex, wrong information given to patient about multiple drugs etc. These were likely to include one or more of immuno-suppressants but that could not be proved as no drug names were listed in these instances. There were five reports regarding medication schemes in general. The nine reports regarding immuno-suppressants and the five reports on medication schemes in general were considered focus points in this project. All together these fourteen reports were reviewed in depth. The remaining 20 were read through but not considered relevant for this project.

Six of the reports were on tacrolimus. Of the remaining three reports on immuno-suppressants, there was one on azathioprine and two on MMF. Of the fourteen reports reviewed in depth, seven of the reports were regarding missed doses. The remaining reports were on multiple medication errors in drug kardex, expired azathioprine found in patients locker, tacrolimus not prescribed, wrong tacrolimus strength given, medication not signed for, wrong information given to patient about medication and wrong drug given.

Table 3: Summary of data from Datix reports regarding immuno-suppressants

Drug name	Description	Lesson learned	Grade
Tacrolimus	At the morning renal ward round it was noticed that the patient had not received her prescribed 22.00 anti rejection medication (tacrolimus). Patient did state that the medication had been withheld.	Medical staff did not prescribe that patient's medication not state that it was to be withheld or pass this information onto nursing staff. Nursing staff did not check with medical staff but assumed drug was to be withheld, which it was to be on this occasion	low
Tacrolimus	Patient founds not to have taken tacrolimus dose. Patient stated he was given the tablets but fell asleep and forgot about them.	Lesson learned missing	Medium

Tacrolimus-prograf	Query wrong dose of tacrolimus-prograf given at morning meds, day staff (bank nurse) signed for 22.00 prograf dose rather than 10.00. Doses different. Query whether patient got 1 mg rather than 0,5 mg at 10.00.	Incorrectly read drug chart	low
Myfortic	On reviewing the drug kardex I noticed that the previous evenings dose of myfortic had not been signed for	Lesson learned missing	
Mycophenolate mofetil	On checking the drug kardex it was noticed that mycophenolate mofetil dose for 20.00 the previous day had not been signed for.	Drug prescribed at handover time and not at time when nursing staff are used to administering medication	low

Tacrolimus	Patient prescribed 13 mg Advagraf at 10 am and was given 13 mg Prograf in error	Incorrect drug administration. Bank nurse unaware of two different preparations of tacrolimus. Drug prescription incorrect, prescribed as Tacrolimus rather than Advagraf (However advagraf stated in column)	low
Azathioprine (AZA)	Expired AZA 50 tablets found in patients locker	Nursing staff not following drug administration policy	low
Tacrolimus	10 pm tacrolimus not prescribed a transplant patient	Medical staff not prescribed routine medications as required daily	low
Tacrolimus	Tacrolimus sent down to haemodialysis room 1 with patient, in order to take at 10 am	Lesson learned missing	low

4.2.2 Staff Interviews

Some of the high risk areas in prescribing and administration identified by staff are listed below.

Table 4: High risk areas in prescribing

High risk areas in prescribing
Not using a suitable kardex i.e. one that has a table for immuno-suppressants on the back
Generic names not used when prescribing
Blood tests assumed to be 12 h troughs when this is not always the case.
Lab tests: getting the bloods to the lab on time
Lab tests: the labs to process it in time
Doctors prescribing the medications in time
Unclear hand writing
Interactions; Prescribing interacting drugs or not noticing when interactions are present.
Reducing immuno-suppression appropriately
Incorrect monitoring
Failure to adjust according to monitoring
Staff on rotation might be relatively inexperienced and/or not used to prescribing immuno-suppressants

Table 5: High risk areas in administration

High risk areas in administration
Generics; not knowing about different formulations
Patient not eating, drinking or vomiting
Patient unable to take the drug orally
Nurses being busy, getting caught up etc
Patient relying on family too much

Formulation, timing of dosing and strength of preparation

Nurses being busy might lead to more errors in terms of switch between drugs and different formulations. Staff were in general very supportive and understanding towards the nurses and their busy schedule. Timing of doses was mentioned as a source of error as it was identified that deviation from set times was bound to occur.

“..when everyone have something prescribed at 10 am and 10 pm, it is impossible for nurses to give everyone their drugs at exactly 10”-junior staff member

Another issue raised was nurses feeling like they were taking over too much of the responsibility for the drugs themselves and that they did not always feel they had the skills for it. One senior nurse mentioned that they had lack of time to sit and educate the patient they way they deserved to be educated and that it would be better for pharmacy to do this part of the patient education.

One comment was made by a doctor who said that it was important for patients to take on responsibility as early as possible for their own medications.

Interactions

All staff considered drug interactions to be important. It was commented that patients might receive interacting drugs when absent from the transplant ward or in the community setting and that this could disrupt their blood levels of immuno-suppressants. It was however emphasised by one senior staff member that if they got a patient that was on a regular dose of an interacting drug, then a dose adjustment might be all that was needed. It was considered a safe and constant interaction and it would not stop the doctor from prescribing either one of the drugs, but it would be taken into consideration at the time of prescribing the initial dose.

In the unit, it was agreed that interactions were taken into consideration. However one staff member stated that this might not always be the case for GPs. It was also mentioned that occasional ones might be missed but the important ones were always considered. One senior nurse commented that the nurses were considered experienced and might also pick up on interactions because they deal with the drugs every day.

One junior nurse mentioned an interesting comment on interactions with food as well and said the reason for prescribing (tacrolimus) at 10 o'clock was so the medications would not interact with each other or food.

“I think they're taken into consideration. They might not always be known. From the GPs point of view, they are reasonable good at calling us if they have a concern or if they're starting new meds. It's quite regular for them to phone and ask “is it ok if we give this?”, but we've been called out a few times particularly with antibiotics like clarithromycin or something like that where that hasn't been discussed with us and they've been put on it. Not just by GPs but by other hospitals. So I think within the unit we're reasonable good, but as a whole it probably could be better.”-senior staff member

Compliance

All staff agreed that adherence to drug regimen was very important in this group of patients. However when asked whether they thought patients did adhere to drug regimens, the responses were variable. Some stated it was variable and others that they thought most patients did adhere.

Interestingly one senior staff member said:

“It depends on how you define adherence. If you mean adherence 90 % of the time they take their tablets around 1 hour around when they’re suppose to, I’d say yes. If your adherence is strict I’d say no.”-senior staff member

Another senior staff member said on the whole patients were compliant especially in the early days, but that there were patients that with time started to get less compliant and it tended to be the ones that did not attend clinic. These patients were considered a worry as they might lose their graft.

When asked why they thought patients might not comply various answers were given. Issues such as patients being worried about side effects, poly-pharmacy leading to confusion and lack of understanding of drugs were listed as potential reasons for non-compliance.

Patient psychology was considered an important issue in compliance. A mix of forgetfulness, impact upon their lifestyle, social factors, stigma attached and genuine mistakes were mentioned.

“I’d say the ones that do and the ones that don’t it’ll be a mixture of forgetfulness and chaotic lifestyle. Other patients are young so I suspect there’s a lot of social factors behind why some people don’t take their immuno-suppression”-junior staff member

Another issue with patients not being compliant was that with the CNI's the dose changed so frequently that it was important that the information kept up with the patient or it could be a potential problem. Another concern with this was that the patient might not have the right tablets for the doses change, so they might need to go to GP and then to community pharmacy who might not have it in stock. This might lead to the patient getting delayed and not changing the dose when they should.

Patient education and documentation

When staff were asked if patients went home with enough knowledge to take their immunosuppressants the way they were intended, patient individuality was highlighted as an important issue. Patient being different in age, culture, co-morbidities and perception of their conditions meant that they should receive education tailored to their needs.

“I think it's important that they have lots of different sources of information so that as well of verbal communication, they need written communication.”-Senior staff member

It was also acknowledged that lack of information could result in patients not taking medication at the right time, with interacting medications or not taking their medication at all. This could ultimately end in graft loss.

Staff were on the whole informed and aware of the education the patients received. They mentioned transplant co-ordinators, nurses, pharmacists, staff nurses, and doctors as the people who educated the patients. The most frequently mentioned were the nurses and pharmacists. One junior doctor did state that most of the education came from pharmacists and that the doctors did not give much education to patients about safely taking immunosuppressants. However one pharmacist did mention that they might not speak to the patient if the patient was being discharged at a weekend or evening.

One junior doctor did not feel that doctors participated enough in giving patient's information:

“We probably don't tell them anything at all really other than what dose to take so from my point of view we don't give them enough information.”-junior doctor

Regarding documentation of education, the nurse's notes on self medication were mentioned as a form for documentation. It was thought by one member of staff that pharmacists “wrote something in their notes”. One senior staff member said that documentation was probably variable. Another senior staff member expressed worries that it might not be documented:

“There's a formal self medication programme which is documented. I have some concerns that it is not (...) We see patients who have passed through the self med programme, and come and clearly don't understand and I think that comes back to what I was saying with individual patients' need to be treated in different ways but the education continues and we reiterate a lot of the purpose and function and reasons behind the immuno-suppressants when they come to the clinic and that's not formally documented but it happens.”-senior doctor

Most staff knew that there was written information given to patients. They mentioned the green book patients get at discharge, nurses handing out information sheets when introducing self medication. These sheets from the nurses had to be read by the patient before self medication started and could also be given to relatives. The discharge script was also mentioned as written information. However, some staff members showed uncertainty about what written information the patients were getting.

Communication

Staff agreed it was very important that the GP was informed about what happened in clinic and hospital;

“Very important, because in effect they’re the ones doing the prescribing. That is also a source of problem; having to convey information to the GP, and that prescription then has to go to pharmacy and pharmacy then have to dispense the medication and each of those steps induces delay and potential error.”-senior staff member

However staff did recognise that there were multiple issues involved in this. One senior doctor stated one of the major issues they had encountered the recent months and years was correspondence with GP because there were concerns around getting clinic letters out in time and they often ended up lagging behind. The GP could then end up receiving different letters at the same time with different doses as there are frequent dose changes in the use of immuno-suppressant to transplant patients. Another problem was if the patient went for repeat prescriptions as the dose might be wrong because it might not be up to date. It could be even worse if there was a change in which drug the patient was on because the patient might not be aware that there had been a change at all. One senior doctor recognised that they as doctors could be better at this and made the suggestion that perhaps if the patient always had their green book with them at it was signed by doctors this might make it clearer.

With regard to the perceptions of consequences about the GP not being informed, staff saw the biggest issue as the fact that patient could receive inappropriate immuno-suppression in the form of too little or too much immuno-suppressants, this again could lead to graft loss. A senior staff member mentioned that he/she had not seen any major consequences and that it was more a matter of time wasting for the GP who had to chase transplant doctors around.

Also mentioned was that patients might find it frustrating; they'd go to the GP and GPs might not be happy to prescribe the drugs so they could often end up coming back to the unit and asking for a hospital prescription. One senior staff member said what would help was if the clinic letters were sent quickly but that it could be several days before a letter was prepared and sent due to lack of secretarial staff. Also he/she said that it would help if the patient was well informed and they had access to a range of tablets and sizes so they could do dose adjustments without having to go through GP. The patient having to wait to go to GP was considered problematic and was not considered a good option.

It was agreed that the GP should have an updated list of medications the patient was on, exactly what drug they were on and the preparation of what drug they were on. Also mentioned by a junior staff member was that they should get an education pack about tacrolimus, the importance of it and the risk factors with it. Staff also thought the GPs should have access to shared care protocols and that they would get information from there. In addition GPs should be informed about what plans the doctors had for changing the immunosuppressants and what was expected from the GPs.

“Transplant is fairly specialised and I don't think the GP will want to know particularly why we've changed doses etc. I just think they need to know the prescription and the dose. I think if there's a switch in medication, there needs to be some explanation to why the switch has taken place as well as the dose that is used, whether that dose will change in time of whether it's a fixed dose forever. So I think they'd like to know if it's likely to change and over what sort of time period.”-senior staff member.

On the question of what information is provided to GP most staff mentioned the discharge letter. This had details of the hospital stay and what drugs the patient was on. Also the follow-up would be included in this letter. The green book that patients receive when doing self

medication was also mentioned. Some staff members did not know many details about the information given to the GP.

“...I’m not sure of what everybody’s practice is in terms of saying that a lot of drugs are going to be stopped at 3 months and altered. I usually say that at 3 months there will be significant changes (...) I’m not sure if there is any other formal information that is given to GP.”-senior staff member

Teamwork

When asking the staff members about who they thought doctors would contact if they were uncertain about anything regarding the prescribing of the drug, the action taken depended on the grade of doctor. Most junior doctors would ask their seniors or the pharmacist. One junior staff member assumed that senior doctors made their own decisions. It was also stated that in the renal unit they might look it up in the renal unit handbook (known as EdRen) as well as ask a more experienced doctor. Staff were in general very supportive of teamwork. They valued their seniors’ opinions as well as other professions’ competence and knowledge.

The pharmacists were valued and both nurses and doctors stated that they frequently asked the pharmacist for advice:

“Speak to the pharmacist! We do that quite regularly. We certainly value the pharmacists and they’re quite rigorous at looking at things up so if we’re uncertain I usually just speak to the pharmacist.”

Staff also looked things up and asked their seniors for advice:

“I suppose depending on the time of day and the need to find the answer, the BNF is available. If not; one of the transplant pharmacists (...) If it’s a middle grade doctor; then one of the senior transplant clinicians.”

Pharmacy in general was also considered a place to seek information and advice:

“Our pharmacist is very much involved with the ward rounds and is on the ward every day and they all know the pharmacist which I’m amazed at which is fantastic. So the pharmacist is our first resource as well as the senior doctors as well... And there’s always the out of hours pharmacy if you every need advice, or anyone else in the other end of the phone which would put you in touch with them.”

4.3 Pharmacist check-list results

		1	2	3	4	5	6	7	8	9	10
Initials											
Ward:		206	206	115	206	206					
type of transplant		Liver	Kidney	Kidney	Kidney+pancreas	Kidney					
Number of days since transplant:		14	1	0	1,5 yrs						
Pharmacist:											
1 Unnecessary drug therapy	a) There is no valid medical indication for the drug therapy at this time										
	b) Multiple drug products are being used for a condition that requires fewer drug therapies										
	c) Drug therapy is being taken to treat an avoidable adverse reaction associated with another medication										
	d) The duration of therapy is too long										
2 Need for additional drug therapy	a) A medical condition requires the initiation of drug therapy	✘	✘								
	b) Preventive drug therapy is required to reduce the risk of developing a new condition										
	c) A medical condition requires additional pharmacotherapy to attain synergistic or additive effects										
	d) The duration of drug therapy is too short to produce the desired response										

3 Ineffective drug	a) The drug is not the most effective for the medical problem																		
	b) The formulation of the drug is inappropriate																		
	c) The drug is not effective for the indication being treated																		
	d) The dosing interval is incorrect																		
	f) Route of administration is incorrect																		
4 Dosage too low	a) The dose is too low to produce the desired response																		
	b) The dosage interval is too infrequent to produce the desired response																		
	c) A drug-drug/food/lab/disease interaction reduces the amount of active drug available																		
5 Adverse drug reaction	a) The drug product causes an undesirable reaction that is not dose-related																		
	b) A safer drug product is required due to risk factors																		
	c) A pharmacodynamic drug-drug/food/lab/disease interaction causes an undesirable reaction																		
	d) The dosage regimen was changed too rapidly																		
	e) The drug product causes an allergic reaction																		
	f) The drug product is contraindicated																		
6 Dosage too high	a) Dose is too high																		
	b) The dosing frequency is too short																		

	c) A drug-drug/food/lab/disease interaction occurs resulting in a toxic reaction to the drug product														
	d) The dose of the drug was administered too rapidly														
7 Inappropriate compliance	a) The patient prefers not to take the medication														
	b) The patient forgets to take the medication														
	c) The patient cannot swallow or self-administer the drug product appropriately														
	d) The time of dosing or the dosing interval is decreasing compliance.														
8 Unclassified i.e. Non-DTP	a) Formulary adherence, e.g. generic switch														

In the liver transplant ward and renal/pancreas transplant ward there were six reports all together five of which were in the kidney transplant ward. *Need for additional therapy, dose too low or adverse drug reactions* were the categories for the interventions recorded.

5 Discussion

5.1 Patient journey

The patient journey allowed the investigator to be able to map the transplant patient's journey. It allowed the investigator to look at a real patient's experiences, co-morbidities, medications and complications in retrospect whilst at the same time looking at guidelines and protocols to see if there were any areas for improvement to minimise risk of harm to the patient. The patient journey also worked as a background so the investigator could get familiar with the journey of a transplant patient through the healthcare system and how the different professions were working together to optimise care for this group of patients. The investigator read protocols and guidelines and attended clinic visits, assessment meetings and ward rounds in addition, to help give a clear picture of how things worked in practice. This allowed the investigator to see how theory was put into practice. The multidisciplinary teamwork was made very clear when attending the ward rounds and the assessment meetings as a range of different professions were allowed to express their opinions. The discussion then took into account every profession's view of each patient. On the ward round meetings the pharmacist's role was emphasised as other professions (mostly doctors) often asked the pharmacist for advice on medications. When spending time on the ward however, it was also clear that nurses found it easy to ask the pharmacist for advice.

When observing the clinic visits (the investigator only attended clinic visits with senior doctors present) it was clear that the doctors were certain of the common concerns around the use of immuno-suppressants. Questions were asked about side effects and all the medications were always gone through with the patients to ensure they were up to date on every medication. For the liver transplant ward's out-patient protocol[19] there exists a memory aid

(one A4 sheet) that can be used in clinic visits. The investigator only attended one clinic visit on the liver transplant ward so it is unknown if this memory aid is often used. There is a potential risk here if decision making is intuitive rather than analytical. The experienced doctors might not feel the need to use the memory aid. However an article written on errors in clinical reasoning states that being older and a more experienced doctor does not guarantee better quality of care or lower risk of reasoning errors[36]. The article also states:

“Irrespective of whether diagnosis or management is the focus, or whether analytical or non-analytical reasoning modes predominate, all decision making is vulnerable to different forms of cognitive and affective (emotional) bias or error.”[36]

This emphasises that there is risk associated with all decision making. However there are ways to minimise these risks for example by every doctor attending clinic always using the memory aid. Therefore it would be of further interest to know if all staff attending clinic visits are aware of the memory aid and if they do use it on a regular basis. It would also be interesting to know how often it has been reviewed and updated.

5.2 Characterising harm assessment

5.2.1 Datix®

The investigator observed when one pharmacist reported on Datix and it was clear that reporting demanded the full attention of the reporter and sufficient time to report so that all information needed would be included in the report. Staff are supposed to get education on Datix when starting a job, however there might be room for improvement in the education on how to use Datix, why to use it, its value and when to report incidents or near misses. There is a lack of standard definitions around what needs to be reported and how the reports are graded and used to improve patient safety. For example one report regarding a missed dose of

immuno-suppressant was graded as medium whilst another regarding an immuno-suppressant that had not been prescribed at all, was graded as low. It might just be that the incident was regarded as low because the likelihood of the pharmacist identifying the error was considered high and so the patient would not come to any harm, however one cannot know this from reading the report alone. This shows how there is a lack of standards for the people investigating the incidents. There needs to be standard definitions of what is considered low, medium and high. All in all, training and information on better use of Datix is needed.

Of the reports reviewed in-depth half of them were regarding missed doses. The missed doses had various reasons for happening; nurse not signed for medication, nurse not given medication, patient fallen asleep, misunderstandings and miscommunications between staff and patient were common explanations. Nurses have a lot to do around the ward and are busy. When medication at times is prescribed at administration times not “normal” to nurses it can be forgotten. The transplant ward has implemented a new procedure to reduce drug errors in administration. The nurse on medicine rounds wears a red vest that says:

“Do not disturb. Nurse on drug round”

This lets the nurses focus fully on what drugs they give each patient and allows them to work without interruption. It would be of further interest to see whether these vests do prevent errors from happening.

One weakness of Datix is that it is subjective in that staff express their own opinion of what happened whilst there might be more than one side to the story. Investigation is however done following the reports. The most important weakness may be the known underreporting going on, which means that the incidents that are reported, might not be representative for what is actually happening. There is a lack of standards for what should be reported on Datix. This

means that staff have different opinions on what should be reported, resulting in subjective viewpoints influencing when staff report incident and when they don't. For example one staff member might only report what he/she considered to be serious incidents, whilst others only report what they consider to be minor incidents. There might also be disagreement about what is considered serious. Furthermore it might vary between different professions what they perceive as serious incidents. Moreover it might just be that reports are reported when convenient to staff. Reports lacking important details are another concern; for example one report did only have the *description* and *action taken*-columns filled out. It was not clear what the problem was or how they handled it. These reports are not complete and have very limited value for using Datix for identifying areas of improvement in a project such as this.

When presenting this project for staff, it quickly became clear how members of staff are not afraid to admit they do not report on Datix. This can be for several reasons. For example staff might not see the benefit of reporting on Datix or they simply don't have time. There is a need for motivation and understanding of purpose if the goal is for everything to be reported on Datix. If everything was reported it would increase the workload for the person in charge of going through reports and there might be need for more staff time to go towards it. If this was to happen there would need to be a clear message as to why it was so important to report incidents or near-misses on Datix. This might also call for increased funding.

The fear of blame would be one matter that would need to be eradicated in order for the focus to be on learning from incidents and not blaming individuals for it. This would involve changing staff's perceptions and attitude towards voluntary reporting which in itself is a challenge. When presenting the topic of this project for them, staff themselves recognised the need for actual data and numbers to back up and assess quality of patient care. At the development and discussion of this project it was clear that there was a huge gap in

knowledge about whether transplant was an area for improvement that needed attention or not, namely because Datix as the one measure for collecting data on incidents was not being used adequately.

5.2.2 Clinical staff interviews

The staff interviews highlighted many high risk areas in administration and prescribing. However the weaknesses to the interviews were that some of the questions asked were long and might have been misinterpreted or misunderstood. The selection of staff was another issue. There were only two nurses whilst there were six doctors. This might have made the interview results biased towards the doctors' opinions and perceptions. If time had allowed it, the investigator could have included staff to the point of saturation. The staff included consisted of a convenience sample however, the results obtained might not have varied very much even if more were included. If more doctors/nurses were included the investigator considers it likely that they would have mentioned many of the same high risk areas that had already been identified. Amongst the senior doctors, there might have been bias introduced as the ones likely to attend and say yes to participate were chosen. This might also have been the ones who were good at following procedures and were confident. This might mean that the sample of people chosen were not representative of all staff in the transplant wards. However it can be considered a strength to this study that doctors who were confident and not afraid to air their opinion were included as they were not afraid to identify weaknesses in the process of prescribing and administration of immuno-suppressants. Not including these doctors, could have lead to fewer high risk areas being identified.

Issues regarding different formulations, timing of dosing and drug interactions

Nurses being busy and having many areas of responsibility was considered an area where errors could occur. Non-nursing staff expressed an appreciation of understanding for this.

Patient taking on responsibility themselves for their medication was considered important in this context. Patients understanding their medications, recognising packages, tablets, formulations etc might help to minimise the risk of administration errors happening. However many patients rely fully on nursing and medical staff, so they might not question them even if they were unsure. One nurse highlighted an important point; the feeling that the nurses were taking over too much of the responsibility for the medications and that did not always have the skills for it. This shows that there might be an area for improvement in terms of increasing the amount and type of education the nurses receive about medications so that they can be confident in administering medications as well as educating patients on them. More pharmacy involvement was suggested in terms of patient education, so that nurses did less educating because the nurses did not always have the time to sit with the patients and educate them. On the other hand the pharmacists do already play an important part in educating the patients on the transplant ward. Pharmacists are however not on the ward at all times, and if patients are discharged on weekends and evenings, they might not be able to meet a pharmacist and so nurses have to do the education. If nurses are not used to this, or don't feel confident in doing it, then it might be that not all patients receive the education they should. More detailed documentation of education could help identify whether some patients don't get the education they should.

Drug interactions were considered important in the administration and prescribing of immuno-suppressants. It was however emphasised by staff that the risk here lied mostly in the community setting. The transplant ward was considered safe in terms of having pharmacists to pick up on interactions as well as clinical staff who were specialised and therefore more aware of many of the common interactions with immuno-suppressants. The GPs prescribing interacting drugs and community pharmacy not being aware of the patients' immuno-

suppressant drugs might lead to community pharmacy dispensing interacting drugs. It was however also stated by a senior doctor that GPs were good at phoning the transplant ward when introducing new medications. The interacting agents most frequently mentioned were antibiotics.

The interactions and communication with GP and community pharmacy is something the investigator would consider important for future investigation. The next step might have been to include the GPs and community pharmacies and put measures in place to see if it improved patient care. It would be of interest to see if drug interactions and communication between community and hospital is a high risk area because it could be prevented by educating and informing staff about patients' medications. Also the liver in and out-patient protocols (appendix 9 and 10) are not possible to access online. The protocols have detailed information about interactions and it could be of benefit to put it online so GP and community pharmacy could access it. This would also ensure that the most up to date version was always available. In addition if patients or GP lose their copy etc, they could access it online. However the disadvantage to this might be that the protocols contain a lot of irrelevant information. The best option might be to update the shared care protocol to include more details or to simply take out relevant information for GPs from the protocols and make it into an information sheet for the GPs.

Compliance

There were several different opinions on whether patients were considered compliant or not. There were many thought reasons for non-compliance. Patient's fear of side effects was one issue. This could be prevented with education and information. Age and forgetfulness amongst patients was another. This could be helped by educating relatives so they could support patients and clear written information to patients in the form of reminders. Also, dose

changing so frequently that patients don't have the right strength at the time of dose change was an issue. Patients might then have to wait for GP to prescribe and then wait for community pharmacy to dispense. This might lead to remarkable delays and ultimately unintended non-compliance by the patient. One suggestion was made that patients should always have a range of tablets and tablets sizes, however, the cost of immuno-suppressants are high and this solution might lead to much wastage and higher costs. One staff member mentioned giving the patients a range of tablets of different strengths. However this could potentially confuse patients and do more harm than good if they end up taking the wrong strengths of tablets. Another important point was that patients were thought to get less compliant as time went by. Here, addressing non-adherence as time went by might be key. Educating patients every so often so they understand that the risk of graft loss remains as time goes by and compliance is always important. This might be best done in the clinic where patients come for check-up and doctors could emphasise the risks of non-compliance. However one senior doctor did state that they did emphasise the importance of immuno-suppressants in clinic:

"(...) we reiterate a lot of the purpose, function and reasons behind the immuno-suppressants when they come to the clinic and that's not formally documented but it happens." Senior doctor

The problem still remaining is that the patients who are non-compliant in their medications might also be the patients that don't attend all their clinic visits. Future work in this would be to assess the patient's perceptions of the education they get, their thoughts around the importance of adherence to immuno-suppressants, their fears about side effects, their illness etc and from this see whether there is an area for improvement here. Also as one senior doctor pointed out, there would need to be a definition to adherence and what good adherence was

considered to be. This might very well vary between doctors, nurses, pharmacists and patients.

Patient education and documentation

There was a large variety in the amount of knowledge the different staff member had on the topic of education. Some knew very little about what education was being given, by who and how it was given. Others were fully aware of the self medication programme with the involvement of the pharmacy and nurses. It was clear that staff in this context did not have knowledge of what other professions roles in the education of patients was. Nurses and pharmacists had sufficient understanding of who was doing the education however there was still the issue that one nurse felt that nurses might be taking over too much of the educating. Most doctors knew about the education patients get, however they were on the whole unaware of the details regarding self administration and the documentation of this. One doctor also mentioned that the doctors were not involved in the education and recognised the lack of information patients got from doctors. However the investigator did attend clinic visits and did observe doctors in the clinic setting educating patients about their immuno-suppressants. One senior staff member stated that it was important for patients to have both written and oral information. The patients do receive both written and oral education through the self medication information sheets and through education from pharmacists and nurses.

Regarding the documentation of self medication, nurse's notes were mentioned as a type of documentation. Several staff members did however state uncertainty about whether it was being documented and the quality of documentation. Nurses and pharmacists documenting the education they give might help clarify what impact this education is having and whether it can be improved upon or not. It would be of further interest to see what type of education is given and by whom. When asked about the written information given to patients, some staff were

unsure whether there was written information given and if so, what type. Most frequently mentioned was the discharge letter that the patients get. This again emphasises that not all staff knew what the other people on the ward were doing. Not knowing the roles of other staff might lead to some staff thinking that one thing is being done when in fact it is not happening.

Further work could be done on the quality of the education given and written information given to patients, a patient's satisfaction survey on the education they receive, their understanding of their immuno-suppressants, the quality of the documentation done and staff's perceptions of other profession's roles on the ward.

Communication

In regards to communication with GPs it was stated that the GPs should have access to shared care protocols and that they would get information from there. However how many GPs actually do access the shared care protocol online remains unknown. It would be of further interest to find this out. It was also said that GPs should be informed about the doctor's plans for changing the immuno-suppressants and what the unit expected in terms of involvement from the GP. However it is difficult for a doctor to inform about plans to change immuno-suppressants as this is done based on a whole clinical picture and many things can influence it. There is no set time frame for when different immuno-suppressants are reduced in dosage or removed except for prednisolone. Although the GPs normally don't initiate or discontinue immuno-suppressants, this does make it a challenge for the GP to keep up as there are no set procedures and times for when this will happen.

The communication with GP was thought to be important, however lacking in detail. There is room for potential errors here. Many staff stated that the risk of interactions were higher in the community setting than on the transplant ward and that this was a risk. Involvement of community pharmacy was not frequently mentioned. More involvement and information to

community pharmacy might reduce risk of interactions happening in community setting as they might pick up on interactions with immuno-suppressants if they knew the patient was on it. Community pharmacy and GP could get a standard information pack about immuno-suppressants and perhaps a copy of the green book. If the green book was always taken to appointments with GP, clinic and community pharmacy it would help minimise risks of errors as an up to date list of medications would always be provided. The patients should be encouraged to use one community pharmacy and this pharmacy could perhaps keep a copy of the green medication reminder book in the patient's file. This would ensure that the community pharmacy was always aware that the patient was on immuno-suppressants before dispensing any other potentially interacting medications. However the limitation to this would be ensuring all copies of the green book were up to date.

Also clinic letters lagging behind due to lack of secretarial staff etc was a problem. This could be solved by more secretarial staff so as to get letters out quickly and minimise risk of GPs getting different letters at the same time. However this would be difficult initially after transplant as clinic visits are frequent several times a week, and it would prove a challenge to get all letters out straight away. Repeat prescriptions were another issue raised as patients might go in with repeat prescriptions and the strength or dose might be wrong. One solution mentioned above would be for patients to always carry the green medication reminder book and always keep it up to date. It could be signed by doctors when updated however sometimes the alterations to drug regimens are given via phone and patients would have to be reminded to make a note in the green book if this was to happen.

The shared care protocol which is available online for GPs was not mentioned by doctors or nurses. This is however a tool that could minimise risk to patients and provide the necessary information to GPs. This should be considered an effective tool to prevent harm, but staff not

mentioning it might mean that not many people are aware of it. If they are unaware of it the chances are that they don't recommend GPs to access it.

Future work on this could focus on GP satisfaction surveys in terms of information given and whether they do use the shared care protocol.

Teamwork

Teamwork is important at the transplant ward. The pharmacists were valued for their contribution. Senior staff were seen as a resource and a place to seek information when uncertainty was present. When staff were asked the question of who they thought a doctor would contact if he/she was uncertain about prescribing of a drug, many mentioned the pharmacist. Some said that the middle and junior grade doctors might look it up somewhere and also ask their seniors, and that the seniors would make decisions themselves. The investigator also attended assessment meetings where the teamwork became clear and the different professions opinions were clearly valued.

5.3 Prospective surveys; pharmacist check-list

The pharmacist check-list included few reports. The recognised issue with clinical pharmacists is how to document what they do without it taking up too much of their time. Pharmacists don't necessarily make interventions but they provide quality assurance checks, this would be difficult to document. One might argue that it is the pharmacist's jobs to make interventions and do checks and so asking them to document everything they do might be asking them to do something that would impact their workload significantly. The pharmacist's job is to capture harm before it happens. It's their job to intervene and prevent harm. Asking the pharmacist to document everything they do would take up a significant amount of their time; time that could be spent on the ward preventing further errors. If the pharmacist's were

to document everything, there would need to be an appropriate system in place for it; a system that was user friendly and that did not take too much of their time. If the pharmacists did have some form of document on what they did it might however be beneficial in showing how valuable pharmacists are in preventing potential errors and costs associated with this.

Weaknesses of the check-list were that it might have been too extensive in spite of the fact that it was simplified prior to use. It required reading and time. The investigator did not go through the check-list before hand with the pharmacists and explanation beforehand might have made it easier for the pharmacists to follow. Also a reason for a low number of interventions recorded might be that the patient numbers in transplant are not that high. Renal transplants are more common than liver, and the few more interventions included here might be reflecting this. However on the whole, liver and pancreas transplants are not that common and so a better solution would have been to do the check-list over a larger time frame, for example a year. This project's time frame did not allow for that to happen.

5.4 FMEA

Although the FMEA could not be carried out due to lack of time, it was clear that there were many high risk areas that were identified through the interviews and the rest of the data collection. Staff were asked about risk and where in the process things were likely to go wrong and so many of the aims of the FMEA were still captured. There were areas identified that were high risk. As further work an FMEA could be done as a follow-up to this project to allow more specific opportunities for improvement to be agreed. The patient journey could be used to map the process and be the basis for an FMEA.

5.5 Strengths of this project

The strengths of this project lay in the use of a variety of different methods to obtain data. The retrospective look at reports from Datix allowed for background information to be given to get an idea as to what types of incidents are happening. The one-to-one semi structured interviews included a range of different professions (nurses, doctors and pharmacists) with different grades of experience (senior, middle grade and junior) and allowed for a range of opinions and hence high risk areas to be identified. The pharmacist check-lists helped the investigator look into actual incidents in terms of what types of reports that came in, which drugs were reported on frequently, how many incidents were reported etc. The case study allowed the investigator get an insight into the patient journey to be able to map the process which was initially supposed to be used to map the process for an FMEA.

6 Conclusion

Areas identified by staff as areas for improvement were in education to patients, education of staff, communication with primary healthcare professions with regard to immuno-suppressants, teamwork amongst the staff on the ward and documentation of interventions and education. The patient journey identified many high risk areas including the following: nurses being busy, interrupted or not giving appropriate education. Patients being non-compliant in medications and follow-up meetings, doctors not having clear handwriting, doctors not writing the formulation of immuno-suppressant clearly (or at all).

Database analysis confirmed that Datix was not a well used reporting system and incidents were mainly in the immuno-suppressant administration category. The incidents reported emphasised the need to follow safe use of medicines policy. The study confirmed that Datix needed to be made more user friendly and less time consuming. There were lack of standards

around grading incidents and there were also unanswered questions around when staff should report and how to report. In addition there was a lack of incentive to report and education is needed to make staff aware of the benefits of reporting in order for everyone to be able to learn from mistakes made.

Pharmaceutical care issues were not well documented and there were no consistent interventions to confirm particular high risk areas. This shed light on the issue that pharmacists rarely document their work. The pharmacist's job is to prevent errors and harm. Therefore it is difficult to demand that all pharmacists document every intervention they do, as this would mean less time was spent on the ward preventing errors.

The richest data came from interviews and highlighted actions that could be used to reduce risk of harm from immuno-suppressive therapy. The data collected can be used to generate an FMEA for agreement and use by a multidisciplinary team.

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8 Appendices

1. Project protocol
2. Ethics approval letter
3. The original check-list from previous pharmacy student
4. Power Point Presentation for Renal and Liver transplant team
5. Interview transcripts
6. Questionnaire
7. My checklist
8. Care issues encountered by pharmacists
9. Pharmacist check-list
10. Patient journey

Appendix 1: Project protocol

Title

A study of the prescribing and administration of immunosuppressant medication in patients receiving liver, kidney and pancreas transplantation

Investigator:

- Kinjal Patel, Master of Pharmacy student, University of Tromsø

Clinical supervisors:

- Katherine Davidson, Clinical Pharmacist RIE
- Scott Garden, Lead Pharmacist RIE

Academic supervisors:

- Moira Kinnear, Head of Pharmacy Education, Research and Development (ERD) and Lecturer in Clinical Practice, University of Strathclyde

Collaborators: Members of multidisciplinary team

Introduction

There are many definitions of harm.

The British Medical Association supports the definition of harm as:

“Adverse outcomes or injuries stemming from the provision of healthcare” [1]

Another definition of the prevention of harm is:

“Freedom from accidental or preventable injuries produced by medical care.”[2]

The Scottish patient safety programme’s (SPSP) [3] objective is to improve the safety of hospital care across the country. The aim is to make the health care system reliable and safe. SPSP is co-ordinated by [4]NHS Quality Improvement Scotland (NHS QIS) which seeks to improve the quality of patient care.

SPSP states that UK and international evidence indicates that 1 in 10 patients experience an adverse event in hospital where adverse events are defined as unintended consequences of care like for example a drug error. Research shows that 50% of adverse events can be avoided if rigorous patient safety processes are routinely followed. Adverse events can result in severe emotional impact on patients, but the costs are also of importance. Adverse events are estimated to cost NHS Scotland around £200m each year in extra treatment and lost bed days.[5] The National Patient Safety Agency calculated that preventable medication errors cost the NHS more than £750m each year in England. [6]

Institute for healthcare improvement (IHI) defines adverse drug events as:

“Harm to the patient from medications, whether or not the result of an error”

Conventional efforts to detect adverse events have focused on voluntary reporting and trying to map errors that do happen. According to IHI, public health researchers have established that only 10 to 20 percent of errors are ever reported and, of those, 90 to 95 % cause no harm to patients [7].

Williams[8] defines medication errors as:

“Any error in the prescribing, dispensing, or administration of a drug, irrespective of whether such errors lead to adverse consequences or not”

He states that medication errors are the single most preventable cause of patient harm. The article also emphasizes the causes of medication errors, one of them being that medical staff responsible for most of the prescribing in hospitals can be relatively inexperienced. Electronic prescribing can be a solution to eliminate the risks of prescribing errors but also has its weaknesses.

Datix

Datix[9] is a software programme that aims to help healthcare workers increase patient safety and reduce harm to patients. Today more than 70 % of the UK NHS use datix. Datix is a safety improvement tool meant to improve patient safety. Any member of staff can report on Datix. However, it is a known weakness that datix is not used consistently in hospitals. Incidents are rarely recorded on datix which makes reports unreliable. One of the problems might be that staff fear blame. It's important to focus on medication error reporting as no-blame processes that are important to improve patient safety. A project carried out by pre-registration pharmacist trainees in 2008 found that[9]:

“Over the total observation period (7 weeks) 3 incidents were documented on the hospital reporting system and 261 medication related incidents were observed by the investigators in the seven specialties.”

One stop dispensing and self administration

One stop dispensing[10] also known as dispensing for discharge essentially means to combine in-patient and discharge dispensing into one process. Along with the use of patients own drugs (POD) this results in quicker discharge by reducing dispensing time, reduced drug errors and reduced wastage (/costs). The use of POD contributes to better drug history as patients are familiar with the packs. Whilst in hospital patients can self administer drugs if clinical staff assess the patients ability to do so as satisfactory. Use of POD contributes to the overall aim of letting more patients self administer their own drugs. Patients will receive education beforehand from clinical staff about self administration and their drugs and are given the chance to ask any questions that might come up.

Immunosuppressant medication[11]

All immunosuppressant medication used in transplant can be considered high risk medication. Transplant patients are a complex group of patients that have a range of different co-morbidities and can be of various ages. Also, graft rejection is dependent on various factors including immune response which is very individual. This makes drug therapy and development of standard protocols for therapy complex to develop and follow. Nonetheless this group of patients need to be especially compliant in drug therapy as non-compliance in worst case scenario can lead to organ rejection and ultimately death.

➤ Antiproliferative immunosuppressants

Azathioprine is widely used for transplant recipients. It is metabolized to 6-mercaptopurine which is further converted to active 6-thioguanine nucleotides. These metabolites are incorporated into DNA where they inhibit purine nucleotide synthesis. Blood tests and monitoring for signs of bone marrow suppression are essential in long-term treatment with azathioprine.

Mycophenolate mofetil is metabolised to mycophenolic acid which has a more selective mode of action than azathioprine. It inhibits purine synthesis but it is specific to lymphocytes. It is licensed for the prophylaxis of acute rejection in renal, hepatic or cardiac transplantation when used in combination with ciclosporin and corticosteroids and is thought to be calcineurin inhibitor sparing.

➤ Calcineurin inhibitors

Ciclosporin and tacrolimus are considered the cornerstones of immunosuppressive regimens. They have similar modes of action. They decrease T-cell activation by inhibiting calcineurin resulting in T-cells that are unable to induce an immune response.

➤ Corticosteroids and other immunosuppressants

Corticosteroids: the use of corticosteroids has gone down because of the advances made in immunosuppressive therapy. They still remain powerful immunosuppressants though and are frequently used in acute rejection and in preventing rejection.

Basiliximab is a monoclonal antibody that prevents T-lymphocyte proliferation; it is used for prophylaxis of acute rejection in allogeneic renal transplantation. It is licenced with ciclosporin and corticosteroid immunosuppression regimens. At the Royal Infirmary of Edinburgh it is used with tacrolimus.

Sirolimus: is a non-calcineurin inhibiting immunosuppressant only licensed for renal transplantation. It is also used in liver transplanted patients. It inhibits T-cell activation via suppression of proliferation driven by interleukin 2 (IL-2) and interleukin 4 (IL-4). Interleukins are a group of cytokine signaling molecules vital to normal immuneresponse. The benefit with sirolimus is that it lacks the nephrotoxicity that is an issue for the calcineurin inhibitors.

Principles of the Failure Modes Effect Analysis (FMEA)[12]

An FMEA is a tool to evaluate a process. It helps identify where the weaknesses (failure points) are, assess these weaknesses and get ideas for improvement so the process is less likely to fail. The steps in the process are:

- 1) Select a process to evaluate with FMEA
- 2) Recruit a multidisciplinary team
- 3) Have the team meet together to list all of the steps in the process
- 4) Have the team list failure modes and causes
- 5) For each failure mode, have the team assign a numeric value (known as the Risk Priority Number, or RPN) for likelihood of occurrence, likelihood of detection, and severity
- 6) Evaluate the results
- 7) Use RPNs to plan improvement efforts

Aim

Develop and validate a tool to inform the analysis of the patient journey (Failure Mode Effect Analysis) and identify opportunities for quality improvement of immunosuppressant medication use.

Objectives

1. Map the patient journey before and after transplantation and identify points which present risk of harm due to potential adverse events associated with immunosuppressant medication use.
2. Characterise the harm assessment based on historical incident reports and recorded interventions. Expand the harm assessment using perceptions of clinical staff
3. Further characterise the assessment using data from prospective survey(s).
4. Validate the FMEA tool by presentation of findings to an expert group.

Subjects and Settings

The project will take place in wards 206 and 117 at the Royal Infirmary of Edinburgh (RIE). The teams on the wards are multidisciplinary and consist of nine consultant surgeons, six consultant hepatologists and ten consultant nephrologists. Also in the wards are nurses,

various grades of medical staff, transplant co-ordinators, a dietician, two pharmacists, a social worker, physiotherapists and psychiatrists who all work together to optimise patient care. Each week the team (and there is one renal team and one liver team) that looks after the ward consist of a junior grade doctor, medical registrar, surgical registrar, consultant physician and consultant surgeon. There is one registrar attached to each team of the liver and kidney teams; one hepatologist registrar, one nephrologist registrar and one surgical registrar. The registrars rotate approximately every two months. One junior doctor is attached to each team and they rotate 4 weekly.

Patients:

1. In-patients only
2. Post-transplant only. Only patients that have had their transplant also including those that have been readmitted for complications of any sort.
3. Transplant patients must be on one of more of the following immunosuppressant medications: Tacrolimus, Ciclosporin, Prednisolone, Mycophenolate mofetil, Azathioprin, Sirolimus or Basiliximab

Clinical staff:

1. Include staff of different grades (senior and junior)
2. Include staff with different duration of experience from the transplant wards
3. Include nurses and doctors in interviews and multidisciplinary team
4. Include the pharmacists from the transplant ward for interviews

Methods

1. Undertake a case study to illustrate the patient journey before and after transplantation and identify potential and actual drug related problems in immunosuppressant drug therapy by doing so. Look into self administration and nurse administration as a potential risk where things can go wrong.
2. Characterise the harm assessment based on historical incident reports and recorded interventions. Expand the harm assessment using perceptions of clinical staff
- 2.1 Characterise harm by using historical Datix incident reports identify which type of drug related problems are associated with immunosuppressant drug therapy, recognising the underreporting in the use of datix. All data will be gathered as one and presented to the FMEA team in the end to discuss and validate the FMEA.

2.2 Expand harm assessment by using clinical staff. Asking the two pharmacists to list the top 3-4 care issues they encounter most frequently. Asking doctors and nurses with different level of experience (Juniors and Seniors) what they think are high risk areas in the process of administration and prescribing of immunosuppressants, that is ask where things are most likely to go wrong.

Administration

- What do you think are high risk areas in the administration of immunosuppressant medication in transplant patients? (That is, are there any particular steps in the medicines administration process where you think things are likely to or could go wrong?)

- The nurses have a lot of responsibility and are busy around the ward. What impact do you think this could have on drug administration to patients?

Do you think procedures are always followed?

- After being discharged, do you think the patients go home with enough knowledge to safely take their immuno-suppressants in the way they were intended?

What are the risks if patients are not educated? Who educates the patient and is there a record of this?

Do you know if there is any written information given to the patient?

- How important do you think patient adherence to drug regimen (compliance) is in this group of patients?
- Do you think most transplant patients do adhere to their drug regimens? If not, why do you think that is?

Prescribing;

- What do you think the risks are in the prescribing of immuno-suppressants to transplant patients?
- Monitoring is important in the use of immune-suppressants, and blood tests are taken frequently. How are the results of the blood tests taken into consideration at the time of prescribing?
- Who (which grade of doctors) does most of the prescribing of immune-suppressants on the ward?

- How important do you think it is that the GP is well informed about what happens in the clinic and hospital? What are your perceptions of consequences if the GP is not being informed?
 - In your opinion, what information needs to be provided to the GP?
 - What information is provided to the GP about current drug regimen at discharge, and eventual changes in drug regimen and how is this documented?
 - At the time of prescribing, do you think drug interactions are taken into consideration?
 - Would you consider drug interactions to be an important issue in the administration and prescribing of immune-suppressants?
 - If at a point in time, the prescribing doctor is uncertain about anything regarding prescribing of the drug, what action do you think the doctor will take?
3. Further characterize the assessment by using data from prospective surveys: Adapt a checklist based on the categorising of common causes of drug therapy problems done by a previous master student[13]. The pharmacists will tick the appropriate boxes. The checklists will be used over a time scale of one month.
 4. Assembling a multidisciplinary group to see if their perceptions are the same as that indicated by the data from the prospective survey(s), the historical data and the perceptions of clinical staff. This will be done by going through the patient journey with the team and having them score each step in regards to how high they feel the risk is of something going wrong (FMEA). Will then see if the FMEA as a tool shows us the same results as the collected data hence if there is consistency between them.
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Appendix 2: Ethics approval letter

South East Scotland Research Ethics Service

Waverley Gate
2-4 Waterloo Place
Edinburgh
EH1 3EG
Telephone 0131 536
9000



Name: Moira Kinnear
Address: Head of Pharmacy Education
Dept of Pharmacy
Western General Hospital
Edinburgh
EH4 2XU

Date: 21/12/2010
Your Ref:
Our Ref: NR/1012AB8
Enquiries to: Alex Bailey
Direct Line: 0131 465 5679
Email: alex.bailey@nhslothian.scot.nhs.uk

Dear Moira,

Full title of project: A study of the prescribing and administration of immunosuppressant medication in patients receiving liver, kidney and pancreas transplantation

You have sought advice from the South East Scotland Research Ethics Service on the above project. This has been considered by the Scientific Officer and you are advised that, based on the submitted documentation (Protocol 4 Kinjal.doc and checklist pharm[1].xls), it does not need NHS ethical review under the terms of the Governance Arrangements for Research Ethics Committees in the UK. The advice is based on the following:

- *The project is an audit using only data obtained as part of usual care, but note the requirement for Caldicott Guardian approval for the use or transfer of person-identifiable information within or from an organisation*
- *The project is an opinion survey seeking the views of NHS staff on service delivery.*

If this project is being conducted within NHS Lothian you should inform the relevant local Quality Improvement Team(s).

This letter should not be interpreted as giving a form of ethical approval or any endorsement of the project, but it may be provided to a journal or other body as evidence that ethical approval is not required under NHS research governance arrangements. However, if you, your sponsor/funder or any NHS organisation feels that the project should be managed as research and/or that ethical review by a NHS REC is essential, please write setting out your reasons and we will be pleased to consider further. Where NHS organisations have clarified that a project is not to be managed as research, the Research Governance Framework states that it should not be presented as research within the NHS.

You should retain a copy of this letter with your project file as evidence that you have sought advice from the South East Scotland Research Ethics Service.

Yours sincerely,

A handwritten signature in black ink that reads 'Alex Bailey'.

Alex Bailey
Scientific Officer

South East Scotland Research Ethics Service

DIFFERENTIATING AUDIT, SERVICE EVALUATION AND RESEARCH

November 2006

The "Ad Hoc Advisory Group on the Operation of NHS Research Ethics Committees" recommended NRES should develop guidelines to aid researchers and committees in deciding what is appropriate or inappropriate for submission to RECs, and NRES (with the Health Departments and with advice from REC members) has prepared the guidelines in the form of the attached table.

RESEARCH	CLINICAL AUDIT	SERVICE EVALUATION
The attempt to derive generalisable new knowledge including studies that aim to generate hypotheses as well as studies that aim to test them.	Designed and conducted to produce information to inform delivery of best care.	Designed and conducted solely to define or judge current care.
Quantitative research – designed to test a hypothesis. Qualitative research – identifies/explores themes following established methodology.	Designed to answer the question: “Does this service reach a predetermined standard?”	Designed to answer the question: “What standard does this service achieve?”
Addresses clearly defined questions, aims and objectives.	Measures against a standard.	Measures current service without reference to a standard.
Quantitative research -may involve evaluating or comparing interventions, particularly new ones. Qualitative research – usually involves studying how interventions and relationships are experienced.	Involves an intervention in use ONLY. (The choice of treatment is that of the clinician and patient according to guidance, professional standards and/or patient preference.)	Involves an intervention in use ONLY. (The choice of treatment is that of the clinician and patient according to guidance, professional standards and/or patient preference.)
Usually involves collecting data that are additional to those for routine care but may include data collected routinely. May involve treatments, samples or investigations additional to routine care.	Usually involves analysis of existing data but may include administration of simple interview or questionnaire.	Usually involves analysis of existing data but may include administration of simple interview or questionnaire.
Quantitative research - study design may involve allocating patients to intervention groups. Qualitative research uses a clearly defined sampling framework underpinned by conceptual or theoretical justifications.	No allocation to intervention groups: the health care professional and patient have chosen intervention before clinical audit.	No allocation to intervention groups: the health care professional and patient have chosen intervention before service evaluation.
May involve randomisation	No randomisation	No randomisation
ALTHOUGH ANY OF THESE THREE MAY RAISE ETHICAL ISSUES, UNDER CURRENT GUIDANCE:-		
RESEARCH REQUIRES R.E.C. REVIEW	AUDIT DOES NOT REQUIRE R.E.C. REVIEW	SERVICE EVALUATION DOES NOT REQUIRE R.E.C. REVIEW

Appendix 3: The original check-list

Taken from Kari Jansdotter Husabø's master thesis "Clinical audit of structured pharmaceutical care plans recorded within a hospital pharmaceutical care service" May 2008

Table 11 ‘Check’ categories coupled to Drug Therapy Problem categories

Check categories	Drug therapy problem categories	Common causes
Medication needs	Unnecessary drug therapy	<p>There is no valid medical indication for the drug therapy at this time</p> <p>Multiple drug products are being used for a condition that requires fewer drug therapies</p> <p>The medical condition is more appropriately treated with non drug therapy</p> <p>Drug therapy is being taken to treat an avoidable adverse reaction associated with another medication</p> <p>Drug abuse, alcohol use, or smoking is causing the problem</p> <p>The duration of therapy is too long</p>
	Need for additional treatment	<p>A medical condition requires the initiation of drug therapy</p> <p>Preventive drug therapy is required to reduce the risk of developing a new condition</p> <p>A medical condition requires additional pharmacotherapy to attain synergistic or additive effects</p> <p>The duration of drug therapy is too short to produce the desired response</p>
Effectiveness	Ineffective drug	<p>The drug is not the most effective for the medical problem</p> <p>The medical condition is refractory to the drug product</p> <p>The dosage form of the drug product is inappropriate</p> <p>The drug product is not an effective product for the indication being treated</p> <p>The time of dosing or dosing interval is not the most effective</p> <p>Route of administration is not the most effective</p>
	Dosage too low	<p>The dose is too low to produce the desired response</p> <p>The dosage interval is too infrequent to produce the desired response</p> <p>A drug-drug/food/lab/disease interaction reduces the amount of active drug available</p>

Table 12 (continued) ‘Check’ categories coupled to ‘Drug Therapy Problem’ categories

Safety	Adverse drug reaction (anticipated/unanticipated)	<p>The drug product causes an undesirable reaction that is not dose-related</p> <p>A safer drug product is required due to risk factors</p> <p>A pharmacodynamic drug-drug/food/lab/disease interaction causes an undesirable reaction that is not dose-related</p> <p>The dosage regimen was changed too rapidly</p> <p>The drug product causes an allergic reaction</p> <p>The drug product is contraindicated due to risk factors</p> <p>The time of dosing or the dosing interval is not the safest.</p> <p>Route of administration is not the safest</p>
	Dosage too high	<p>Dose is too high</p> <p>The dosing frequency is too short</p> <p>A drug-drug/food/lab/disease interaction occurs resulting in a toxic reaction to the drug product</p> <p>The dose of the drug was administered too rapidly</p>
Compliance	Inappropriate compliance	<p>The patient prefers not to take the medication</p> <p>The patient forgets to take the medication</p> <p>The drug product is too expensive for the patient</p> <p>The patient cannot swallow or self-administer the drug product appropriately</p> <p>The drug product is not available for the patient</p> <p>The time of dosing or the dosing interval is decreasing compliance.</p>
	Unclassified i.e. Non-DTP	Formulary adherence, e.g. generic switch

Appendix 4: Presentation of project for transplant ward

Project title

A study of the prescribing and administration of immunosuppressant medication in patients receiving liver, kidney and pancreas transplantation

Supervisors and collaborators

- ▶ Academic supervisors
 - Steven Hudson; Professor of Pharmaceutical Care, University of Strathclyde
 - Moira Kinnear; Head of Pharmacy Education, Research and Development and Lecturer in Clinical Practice, University of Strathclyde
- ▶ Clinical supervisors
 - Kathryn Davidson; Clinical Pharmacist, HE
 - Susan Green; Lead Pharmacist, HE
- ▶ Collaborators and members of multidisciplinary team will of course be acknowledged in the thesis

Project aim

- ▶ Develop and validate a tool to aid the analysis of the patient journey and identify opportunities for quality improvement of immunosuppressant medication use

Objectives

1. Identify points where there is potential for harm resulting from use of immunosuppressant medication
2. Identify and quantify these risks using retrospective incident reporting (i.e. Datix) and recorded pharmacist interventions
3. Expand the harm assessment using perceptions of clinical staff
4. Further characterise the assessment using data from prospective survey(s)
5. Validate the FMEA tool by presentation of findings to an expert group

Failure Modes Effect Analysis (FMEA)

- ▶ An FMEA is a tool to evaluate a process systematically. It identifies where the process might fail and helps to assess the impact of these failures.
- ▶ Steps in the process
 - Failure modes (What could go wrong?)
 - Failure causes (Why did the failure happen?)
 - Failure effects (What could be the consequences of each failure?)

Steps to conducting an FMEA

1. Select the process to evaluate with the customer
2. Recruit a multidisciplinary team
3. Have the team meet together to list all of the steps in the process
4. Have the team list failure modes and causes
5. For each failure mode, have the team assign a numerical value (known as the Risk Priority Number or RPN) based on likelihood of occurrence, likelihood of detection, and severity
6. Evaluate the results
7. Use RPNs to plan improvement efforts

Methodology

1. Identify points where there is potential for harm by conducting a case study to illustrate the patient journey
2. Historical incident reports from Datix and recorded pharmacist interventions will be used to characterise the harm
3. Interviewing and shadowing clinical staff to understand harm prevention
4. Gain an expert multidisciplinary team to validate the Failure Modes Effect Analysis (FMEA) as a tool

Appendix 5: Staff interview transcripts

Staff's answers to interview questions

Participant 1; junior doctor

Administration

1. What do you think are high risk areas in the administration of immunosuppressant medication in transplant patients? (That is, are there any particular steps in the medicines administration process where you think things are likely to or could go wrong?)

Suppose there's a couple of things...first of all transplant patients aren't always admitted to transplant wards so they tend to go to other wards to start with anyway before they're referred to us. When people aren't used to looking after immuno-suppressants they either prescribe it at the wrong time or they don't prescribe it at all or they don't to levels. Or they do levels but the levels are done at the wrong time, they're not trough values. I suppose another problem with the administration is when they use the wrong brand so the wrong preparation so they'll use advagraf instead of prograf or give advagraf twice daily. So I'd say they are the quite common things that could go wrong. I suppose other times is to do with the problem in administration would be when the patient is either not eating or not drinking or vomiting and is unable to take it orally.

2. The nurses have a lot of responsibility and are busy around the ward. What impact do you think this could have on drug administration to patients?

Do you think procedures are always followed?

I think we're generally very good. Remember everybody has got it prescribed at 10 o'clock, ten in the morning at 10 at night and it's impossible for them to give it to everybody at 10 o'clock because there's lots of patients, but I think the really do try to spread it between 10 and twenty passed. And I think immuno-suppression in this ward anyway is definitely prioritized to be given. So I think it's probably done all right. The other issue it the Mycophenolate and Tacrolimus have to be given at different times, two hours apart and that's not always done in other wards.

3. After being discharged, do you think the patients go home with enough knowledge to safely take their immuno-suppressants in the way they were intended?

I have no idea! I would think so. I would hope so because they are very carefully counseled at the clinic and they get sent home with a booklet and with information leaflets and information packs which they read and usually the nursing staff would insure that they're taking their tablets independently before they're discharged. So, I think a great effort is made to make sure that they know what they're taking and how to take it and certainly I think one of the prerequisite to getting a kidney transplant is being able minded enough to comply with the treatment post transplant so I'd like to think that was done pretty well.

What are the risks if patients are not educated?

They will either take too much which is quite renal toxic and they cause hyperkalemia so they'll either get renal failure or hyperkalemia which is dangerous or they'll take too little and end up with vascular rejection so those are the problems, yeah.

Do you know who educates the patient and is there a record of this?

The education is definitely done by the nurses. I suspect the pharmacist is involved as well. The doctors certainly aren't involved in educating the patient. I don't think I'm qualified to educate patients on anything to be honest. I don't think or don't know if there is any formal documentation being done.

4. How important do you think patient adherence to drug regimen is in this group of patients?

It's absolutely paramount. It's an essential part of the long term success of a transplant graft.

5. Do you think most transplant patients do adhere to their drug regimens? If not, why do you think that is?

I think it's extremely variable. I'd say most of them do. It's very difficult for me to tell. I'd say the ones that do and the ones that don't it'll be a mixture of forgetfulness, chaotic lifestyle. Other patients are young so I suspect there's a lot of social factors behind why some people don't take their immuno-suppression.

Prescribing

1. What do you think the risks are in the prescribing of immuno-suppressants to transplant patients?

Ehm, when you're prescribing on the kardex, first of all you need to use a kardex which has got a table on the back for the immuno-suppressants and they're not always available in other wards. They are always available in this ward. Second thing is when you're actually prescribing, you prescribe it by either prograf or advagraf, generic names. You can't write tacrolimus or else they get the wrong preparation. You need to write on the actual prescription dose as charted not a normal dose. Quite often when they come into a ward that wasn't the transplant ward they often seen the patient takes 400 mg of tacrolimus twice daily and they'll prescribe that at prograf 400 twice daily and that will be given when actually it should be written as "as charted" because the dose is variable depending on what their levels are, and diarrhea etc etc.

2. Monitoring is important in the use of immuno-suppressants, and blood tests are taken frequently. How are the results of the blood tests taken into consideration at the time of prescribing?

Well we routinely do levels Monday, Wednesday and Friday and every time a level is done, it's checked that afternoon and there's an alteration made to the drugs. Sometimes we slightly pre-empt that. If a patient is going on to something like fluconazole we'll pre-empt the level

and ignore the level, but half the dose of tacrolimus expecting that it will go up when the patient takes fluconazole. So I would say it's taken into account every time.

3. Who (which grade of doctors) does most of the prescribing of immuno-suppressants on the ward?

The registrar will do most of the prescribing but the levels will be looked at by a consultant every day that they are done.

4. How important do you think it is that the GP is well informed about what happens in the clinic and hospital?

I'd say it's extremely important but it's such a specialist area, it would be very difficult for the GP, or anybody who is not working in transplant to be able to make good decisions about immuno-suppression. So it's very important that they're informed about what's going on at the same time any decisions that need to be made, should be done by the transplant team.

What are your perceptions of consequences if the GP is not being informed?

I've not come across any consequences of GPs not being informed, yet. Probably because I work in the ward not in the out-patient clinics. So I do a lot of discharge for this group of patients but I've not come across a disaster yet where GP hasn't been informed.

5. In your opinion, what information needs to be provided to the GP?

The fact that the patient is on it, exactly what drug they're on and preparation of what drug they're on. All the blood are done at the transplant clinics here pretty much rather than the GP so what investigations need to be done and when the patient is next going to be seen.

6. What information is provided to the GP about current drug regimen at discharge, and eventual changes in drug regimen and how is this documented?

The patient gets the formal discharge letter which I do and that details what's happened during the patients admission and what changes there are in the patients drugs. A full list of their current medication doses and usually what follow up has been arranged for them. So that's what formal documentation they will get.

7. At the time of prescribing, do you think drug interactions are taken into consideration?

Yes

8. Would you consider drug interactions to be an important issue in the administration and prescribing of immuno-suppressants?

Extremely. Occasionally it does happen when a patient that's not in the ward is given clarithromycin or fluconazole or something in the community and it's disrupts their immuno-suppressant levels so I'd say it's an absolutely essential.

9. If at a point in time, the prescribing doctor is uncertain about anything regarding prescribing of the drug, what action do you think the doctor will take?

Depends on the grade of doctor. So I would phone my registrar or the pharmacist. My registrar would speak to his consultant or the pharmacist and the consultant would usually make their own decision.

Participant 2: middle grade doctor

Administration

1. What do you think are high risk areas in the administration of immunosuppressant medication in transplant patients? (That is, are there any particular steps in the medicines administration process where you think things are likely to or could go wrong?)

I think one area is confusion between once daily and twice daily preparations so prograf and advagraf. People not appreciating that if they switch to advagraf they need to take same overall dose which would be twice the dose of prograf at that time. Issues relating to generic prescribing and issues relating to timing of administration of immuno-suppression. Issues regarding levels and when levels are taken relative to when drugs are taken and also people prescribing medications like antibiotics who are unaware of the effect that could have on the levels of CNI's for example.

2. The nurses have a lot of responsibility and are busy around the ward. What impact do you think this could have on drug administration to patients? They might make mistakes and give the wrong drugs or the wrong dose to people. Also the timing of administration may be delays in when people get their medication if they are busy.

Do you think procedures are always followed?

I think the nurses do their best to follow procedures and to minimize errors but it's not infallible.

3. After being discharged, do you think the patients go home with enough knowledge to safely take their immuno-suppressants in the way they were intended?

Most patients.

What are the risks if patients are not educated?

That they'll take the wrong immuno-suppression at the wrong time. That they'll not take their medication when they're supposed to, that they'll not know that they need to be careful about other medications interacting with immuno-suppressant. And that they would attend follow ups appropriately.

Who educates the patient and is there a record of this?

I think the doctors nurses and pharmacists will all and transplant co-coordinators will all be involved in educating the patient. And I think probably the documentation would be variable.

Do you know if there's any written information given to the patient?

I think they get written information. They should routinely get written information about their immuno-suppressants.

4. How important do you think patient adherence to drug regimen (compliance) is in this group of patients?

Very important

5. Do you think most transplant patients do adhere to their drug regimens? If not, why do you think that is?

I think most don't 100% because of impact upon their lifestyles, genuine mistakes, forgetfulness, stigma attached and wanting to de-medicalise their problems.

Prescribing

1. What do you think the risks are in the prescribing of immuno-suppressants to transplant patients?

Patient getting drug toxicity, being over immuno-suppressed and patients being under immuno-suppressed and being at risk of rejection.

2. Monitoring is important in the use of immuno-suppressants, and blood tests are taken frequently. How are the results of the blood tests taken into consideration at the time of prescribing?

Well we look at renal function in terms of creatinine, looking at the full blood count in terms of if there is any bone marrow suppression and also looking at the drug levels in order to determine if someone is receiving too much or too little immuno-suppression.

3. Who (which grade of doctors) does most of the prescribing of immuno-suppressants on the ward?

I think in clinic that is either consultant or registrar, on the ward then the decision is usually consultant or registrar although the signature in terms of the prescription may be someone more junior.

4. How important do you think it is that the GP is well informed about what happens in the clinic and hospital?

Very important

What are your perceptions of consequences if the GP is not being informed?

It increases the likely hood of the patient receiving inappropriate immuno-suppression.

5. In your opinion, what information needs to be provided to the GP?

They need to understand the rationale for immuno-suppression and they need to appreciate that other medication can interfere and they should feel that we in the renal unit want to be contacted if they have any questions at all. I much rather be contacted by something trivial rather that have to deal with the consequences and mistakes later on.

6. What information is provided to the GP about current drug regimen at discharge, and eventual changes in drug regimen and how is this documented?

When the patient is discharged after having a transplant they get a discharge letter, a letter after every admission and they get a letter after every clinic appointment. If changes need to be made sooner or more urgent changes then there may be communication by telephone.

7. At the time of prescribing, do you think drug interactions are taken into consideration?

In hospital and transplant unit, yes. GP: not always

8. Would you consider drug interactions to be an important issue in the administration and prescribing of immuno-suppressants?

Very important.

9. If at a point in time, the prescribing doctor is uncertain about anything regarding prescribing of the drug, what action do you think the doctor will take?

Within renal transplant unit, the doctor would either ask a more experienced doctor or would look up in the renal drug handbook or both.

Participant 3; senior doctor

Administration

1. What do you think are high risk areas in the administration of immunosuppressant medication in transplant patients? (That is, are there any particular steps in the medicines administration process where you think things are likely to or could go wrong?)

Incorrect formulation, incorrect dose, inappropriate times of taking medication, incomplete (noise), poor compliance

2. The nurses have a lot of responsibility and are busy around the ward. What impact do you think this could have on drug administration to patients? Do you think procedures are always followed?

Incorrect timing- They can't go around and do the drug round at the appropriate time. Mistakes in drug prescription such that they get the dose wrong. If we switch between

advagraf and prograf, there may be confusion relating to that. If nurses are too busy to check what formulation of tacrolimus they're on then the wrong formulation may be provided. Do I think they always adhere to? No.

3. After being discharged, do you think the patients go home with enough knowledge to safely take their immuno-suppressants in the way they were intended?

Some but certainly not all and in fact we have a number who are clearly not able to take it appropriately and probably will never ever be able to take it appropriately.

What are the risks if patients are not educated?

Poor compliance in its broader sense leading to under immuno-suppression and over immuno-suppression and it's not just the immuno-suppressant effects. We've had people taking the wrong dose and having marked renal dysfunction with tacrolimus.

Who educates the patient and is there a record of this?

Nursing staff educate the patients with the involvement of pharmacy. There is a formal record and 3 step process.

Is the patient given any written information?

Yes

4. How important do you think patient adherence to drug regimen (compliance) is in this group of patients?

Very

5. Do you think most transplant patients do adhere to their drug regimens? If not, why do you think that is?

I think it's the degree of compliance rather than the absolute non-compliance and people comply poorly for a number of reasons. Young patients may not comply because they're too busy doing other things, they think they're immortalized and by missing a few drugs it's not going to matter. They may be worried about the side effects of steroids. People used to get worried about the side effects of cyclosporine. In general as patients get further from their transplant, if they've had no complications they probably feel that the immuno-suppression is less important and compliance will drop off. It's easy to forget medications, I do it. If they are old, there may be confusion, and there may be difficulties with poly-pharmacy. And as I said there are some people who I don't think ever come to grips with what medication they should be taking and why. And if they don't see it as vital, don't understand it, then compliance will be reduced so I don't think there's one factor, there's lots of factors and it can vary between patients.

Prescribing

1. What do you think the risks are in the prescribing of immuno-suppressants to transplant patients?

I suppose if we take tacrolimus there's getting the correct formulation, prograf versus advagraf. Incorrect doses, incomplete monitoring and failure to adjust appropriate with that. And not reducing immuno-suppression at the correct time. Immuno-suppression is at its greatest level immediately after a transplant, right after an episode of rejection, and should reduce over 3 month period, but often it doesn't or it doesn't do it in a timely fashion. There's a possibility of drug interactions. We've had patients that have been treated with erythromycin for chest infections even on the transplant ward. Very high tacrolimus levels after that.

2. Monitoring is important in the use of immuno-suppressants, and blood tests are taken frequently. How are the results of the blood tests taken into consideration at the time of prescribing?

Not quite certain about the question... I suppose we do have a protocol which guides the tacrolimus level, and what targets are made for different times out from the transplant. Do understand it's a guide, so on the liver side we probably use lower levels than are in the protocol and there are a number of factors which will feed into any decision about switching the tacrolimus dose, duration out from transplant and ongoing complications, renal dysfunction, any problems with hyperkalemia. The other immuno-suppressant that we may be using such as MMF versus azathioprine, so the global burden of immuno-suppression and what we're trying to achieve. What the indication for transplant was. Hepatitis C we try and run lower rather than higher levels, but not so low that we get rejection. Patient age may come into it again. Higher levels for younger patients and of course what we think is happening with the liver function test. So the level we get back is not an absolute trigger for a response in changing the tacrolimus dose, it's another bit of information along with the rest of the patients to make a decision for dose modification.

3. Who (which grade of doctors) does most of the prescribing of immuno-suppressants on the ward?

Prescribing and writing the cardex'es; registrars and FY2's

4. How important do you think it is that the GP is well informed about what happens in the clinic and hospital? What are your perceptions of consequences if the GP is not being informed?

I think it is very important. Partly 'cause they're terrified of immuno-suppression and really worried about what it is and what it means and making any changes and they probably shouldn't be making any changes. I think the important thing for them is to be aware what the drug is, what the side effects are and adverse drug reactions they should be looking out for

and being aware of drug interactions for their own safe prescription. So, not prescribing a macrolide antibiotic in the setting of a chest infection.

5. In your opinion, what information needs to be provided to the GP?

All GPs should have or do have access to shared care protocols for most of immunosuppression. It's historical; we don't actually have a shared care protocol for azathioprine. That's historical, it's been used for so long we've not developed one for transplantation alone. So they have information from there, they need timely knowledge about what immunosuppression they're on, I suppose what plans we would ordinarily have for changing immunosuppression and what was expected from them. Do they always get it? I don't think so.

6. What information is provided to the GP about current drug regimen at discharge, and eventual changes in drug regimen and how is this documented?

Not enough, I suspect. I suspect we don't document it. Answer is I don't know.

7. At the time of prescribing, do you think drug interactions are taken into consideration?

Here in the unit? Yes.

8. Would you consider drug interactions to be an important issue in the administration and prescribing of immunosuppressants?

Yes

9. If at a point in time, the prescribing doctor is uncertain about anything regarding prescribing of the drug, what action do you think the doctor will take?

Will take or should take? I suppose depending on the time of day and need to find the answer, the BNF is available. If not; one of the transplant pharmacist, if not; if it's a middle grade doctor; then one of the senior transplant clinicians.

Participant 4; senior nurse

Administration

1. What do you think are high risk areas in the administration of immunosuppressant medication in transplant patients? (That is, are there any particular steps in the medicines administration process where you think things are likely to or could go wrong?)

I think the fact that sometimes patient education is not the best and they don't understand the importance of them. And we have old patients who, I wouldn't say they're non compliant... the majority of patients are, but you have the odd patient that perhaps doesn't understand. We had one particular gentleman I can think of that relied on his family to do his medication. So I think there are dangers there, and perhaps they need a bit more education and input on the importance of them. There can be dangers there, if they don't understand the rationale behind why they need to take them really.

2. The nurses have a lot of responsibility and are busy around the ward. What impact do you think this could have on drug administration to patients? Do you think procedures are always followed?

I think as the years have gone by, pharmacy...we have a wonderful pharmacist on the ward don't get me wrong, but she's one person for many people, and as the years have gone on, nurses take on a wee bit more of this role, a wee bit more of that role..and pharmacy...I've been away from 18 months and come back, and I'm amazed that you have to now count the tablets on the script, you have to administer to the patients, you have two of you to check, which is fine..ehm, you have to dispense the medicines yourself which we've been doing for a few years, whereas before, you did a letter than went to pharmacy so that was taken away from you. I think in transplant, a huge part of our role is to educate the patients on their needs and for years patients have been doing self medicine in transplant, so it is very much part of our role, but a huge input from pharmacy would be far better for patients because they're getting the correct advice. Because you guys have the experience and knowledge that we don't. And also we don't have the time to sit with patients and educate them the way that they ought to have, we don't always have time to do it the way that it should be done.

3. After being discharged, do you think the patients go home with enough knowledge to safely take their immuno-suppressants in the way they were intended?

I would hope so, yes. There's one particular gentleman I'm thinking about. We decided that he needs a dosette box for his MMF and tacrolimus, so that they could go in there. We would send patients home if we didn't feel it was safe bit at the same time we can't keep them in hospital just 'cause they don't have the knowledge of their tablets, but I think education would certainly more what the patient needs-from the pharmacy team.

What are the risks if patients are not educated?

The first thing is rejection because it's important to take their immuno-suppressants to prevent their organ rejection. It is life threatening if they don't comply.

Who educates the patient and is there a record of this?

Well yeah, the nurses educate them and the transplant co-ordinators have a big role with medication. I suppose we do have it documented. We have paperwork for patients that do self-med and we have stage 1, 2 and 3. We can consent them if we deem them fit to do self meds unsupervised so we do have documentation to support the safety of things and we also document it in the nursing notes that patients are on self med and things like that.

Is the patient given any written information?

Yes, when they go home they have their green books that tell them what the medication is for, why their taking them etc. They have it all written down, and how often they take them and what they take them for.

4. How important do you think patient adherence to drug regimen (compliance) is in this group of patients?

It's paramount. If you do nothing else, at 10 in the morning you do your tacrolimus right, and ten at night.

5. Do you think most transplant patients do adhere to their drug regimens? If not, why do you think that is?

Oh yes, evidently they do. You get so many patients that are so grateful for having given them their life back. You have an odd patient, that, I'm not saying they don't comply but it depends on the culture of people as well. We have one gentleman and his culture is that his family does everything for him. He's a young man, he's fit, he's well, he's healthy, he's nursed back to health fully independent, but I know his family will do everything for him.

Prescribing

1. What do you think the risks are in the prescribing of immuno-suppressants to transplant patients?

I would hope it never would but it's like with any drug administration, the writing is eligible and if you don't have the knowledge behind what you're doing, that's a danger already. But the majority of nurses do have the knowledge of what they're dispensing and if they don't, they have the BNF to look it up.

2. Monitoring is important in the use of immuno-suppressants, and blood tests are taken frequently. How are the results of the blood tests taken into consideration at the time of prescribing? Not asked as not relevant for nurse.
3. Who (which grade of doctors) does most of the prescribing of immuno-suppressants on the ward?

FY1 but in transplant FY2, under supervision of consultants etc

4. How important do you think it is that the GP is well informed about what happens in the clinic and hospital?

Very important. Everybody who has responsibility for the patients has a bit of knowledge about what is going on. Transplant is so specialized, there's enough people out and about there, and enough information for people to be able to understand how important it is that these patient have things just so, but it's very evident, that if any patient anywhere in Scotland becomes unwell even if they have a chest infection, or a fractured hip, no matter what's wrong with them: if they've had a transplant, they come back to us because they are very specialized patients. And that's nice, you get to follow up, but yes the GPs are very good at lifting the phone and asking for advice, as are relatives and patients. You're a resource to

everybody really. But yeah, I think there's quite a lot of good information that goes out to GPs.

What are your perceptions of consequences if the GP is not being informed?

I can't answer that. I'm not at the other end. I don't understand fully what the information lacking would be. I would hope there was enough information for them and if not they would have to phone.

5. In your opinion, what information needs to be provided to the GP?

They always have the discharge script with their letter, with their medication. The GP has a more detailed letter that the registrars and the consultants have written. They give information about what's been happening so they should be well enough informed. Now in Lothian we have tracks so GPs can access blood results and things from the track statement

6. What information is provided to the GP about current drug regimen at discharge, and eventual changes in drug regimen and how is this documented? Did not ask question as she answered that above.

7. At the time of prescribing, do you think drug interactions are taken into consideration?

I would hope so. A lot of nurses are very experienced. We have the knowledge that give certain drugs together. I think they (the nurses) would know because they deal with it those drugs every day.

8. Would you consider drug interactions to be an important issue in the administration and prescribing of immuno-suppressants?

Absolutely

9. If at a point in time, the prescribing doctor is uncertain about anything regarding prescribing of the drug, what action do you think the doctor will take?

They're very good at phoning the registrars who have the advice. Our pharmacist is very much involved with the ward rounds and she's on the ward every day and they all know her which I'm amazed at which is fantastic. So she's our first resource as well as the senior doctors as well. And there's always the out of hours pharmacy if you ever need advice, or anyone else in the other end of the phone which would put you in touch with them.

Participant 5; junior nurse

Administration

1. What do you think are high risk areas in the administration of immunosuppressant medication in transplant patients? (That is, are there any particular steps in the medicines administration process where you think things are likely to or could go wrong?)

In the timings when we give it. If we don't have in prescribed on time, that can go wrong and they're getting it late. Also with giving it at 10, you might not give it bang on ten if you get tied up, so that's really the major issues.

2. The nurses have a lot of responsibility and are busy around the ward. What impact do you think this could have on drug administration to patients? Do you think procedures are always followed?

We try to follow them, but if you get tied up with a patient and you can't get away or if something major happens, it is pretty hard to give it on time.

3. After being discharged, do you think the patients go home with enough knowledge to safely take their immuno-suppressants in the way they were intended?

Yes, they're seen by us (the staff nurses), the doctors and pharmacists as well and the pharmacists are pretty good at giving the talks before they go home, so yeah I think so.

What are the risks if patients are not educated?

If they're not educated the risks are: are they taking the right dose at the right time and not with their other tablets 'cause they have interactions. You do sometimes see them coming in and they're just swallowing them with every other tablets they're due.

Who educates the patient and is there a record of this?

Staff nurses educate them, there's a record of that when we give the self medication, then the pharmacists educate them as well and they write something in the notes about doing so.

Is the patient given any written information?

Yes, when they get their self medication, we hand out education sheets and they can read that in their leisure and we give that out before we sign so they can't do it without reading the information we give them. We also give that to the relatives if required so they are educated about the importance of the tablets too.

4. How important do you think patient adherence to drug regimen (compliance) is in this group of patients?

It really depends on the patients and their attitudes. Some patients are fantastic and they'll all say bang on ten o'clock and other patients are less likely to want to take their tablets. It's all down to the patient really.

5. Do you think most transplant patients do adhere to their drug regimens? If not, why do you think that is?

Yeah, they know the importance of them.

Prescribing

1. What do you think the risks are in the prescribing of immuno-suppressants to transplant patients?

Getting the bloods to the lab on time, the labs to process it in time, and then the doctors to prescribe it in time. There's been numbers of times when you're chasing everyone up just to try and get the dose prescribed so that is really where things can go wrong.

2. Monitoring is important in the use of immuno-suppressants, and blood tests are taken frequently. How are the results of the blood tests taken into consideration at the time of prescribing? Not asked as not considered relevant for a nurse.
3. Who (which grade of doctors) does most of the prescribing of immuno-suppressants on the ward?

It's our senior house officer or registrars who do it.

4. How important do you think it is that the GP is well informed about what happens in the clinic and hospital?

It is really important because the GP sometimes aren't aware of the Tacrolimus and prograf and everything else. They don't realize the importance of that to the transplant patients (noise)

What are your perceptions of consequences if the GP is not being informed?

The GP can change the tacrolimus, too high dose, too low dose and they lose their graft.

5. In your opinion, what information needs to be provided to the GP?

They need an education pack about tacrolimus etc and the importance, the risk factors with it, just a bit more education for them I suppose because it's a specialized drug.

6. What information is provided to the GP about current drug regimen at discharge, and eventual changes in drug regimen and how is this documented?

When we give the discharge letter, it should say in it that they shouldn't touch the tacrolimus and that it will be done at clinic, but I don't know if it that actually does happen. Also we have a green book that we give out to patients in self medication. It does state in that for the GP not to alter the dose without corresponding into the hospital.

No don't know how this is documented.

7. At the time of prescribing, do you think drug interactions are taken into consideration?

Yeah, that's why it's prescribed at 10 o'clock so it's not interacting with the morning meds or the food. And again it's down to the doctors to see if they're on any tablets that interact.

8. Would you consider drug interactions to be an important issue in the administration and prescribing of immuno-suppressants?

Definitely, if you don't watch what you're prescribing, it won't work as well.

9. If at a point in time, the prescribing doctor is uncertain about anything regarding prescribing of the drug, what action do you think the doctor will take?

They quite often phone our pharmacists that we have in transplant. The pharmacists are brilliant, so they'll tell you.

Participant 6; senior doctor

Administration

1. What do you think are high risk areas in the administration of immunosuppressant medication in transplant patients? (That is, are there any particular steps in the medicines administration process where you think things are likely to or could go wrong?)

I suppose there's the predictable and unpredictable consequences of prescribing immuno-suppressants. You're immuno-suppressing patients so you've got the risk factors like infection, malignancy, drug toxicity, graft dysfunction. You've got the unpredictable consequences due to either prescribing errors or patient adherence to prescribed regimes. Drug interactions, intercurrent illnesses, infections and things like that. So you know it can be a consequence of inadequate communication, miscommunication or insufficient communication.

2. The nurses have a lot of responsibility and are busy around the ward. What impact do you think this could have on drug administration to patients?

Do you think procedures are always followed?

I think patient administration is only a small part of the whole patient journey, but yes, very definitely it can have an effect. We see that the timing of prescribing of immuno-suppressants: we advocate for drugs like prograf or neoral 10pm and 10am and that doesn't fit in with the drug prescribing round, so instantly there is a problem. I think it's very important to encourage patients as early as possible to take on the responsibility for their medications. They need to have the information and understanding to be able to do that. I think there are other risks obviously with many patients in a ward and obviously drug errors in terms of administration but I think those can be reduced, particularly where patients are keeping their own drugs rather than having trolleys. So I think there are things that are improving but a busy ward is not particularly conducive environment for safe prescribing.

3. After being discharged, do you think the patients go home with enough knowledge to safely take their immuno-suppressants in the way they were intended?

Some patients do, some patients don't. Patients are all individuals and it's very clear to us in the clinic that some have got a very good understanding and are very on top of it, whilst others don't, so having any set protocol pathway for educating patients about medication has to respect those patients' differences. Some find it incredibly hard and there are patients who clearly are never going to cope. They may even come into a transplant relying on dosette boxes and therefore they just don't have the capacity to take on the intricacies of prescribing immuno-suppressants. I think you have to adjust what you do for individual patients. I think it's important that they have lots of different sources of information so that as well of verbal communication, they need written communication. I think one of the big issues about transplant patients particularly the prescribing of CN and phosphatase inhibitors is that they change so frequently, it's important that that information keeps up with the patient and that is a source of problems. What we often see is that by the time the discharge letter reaches the GP, the patient has already been to the clinic once or twice and a couple of dose changes have already happened and suddenly the GP is hit with two bits of information coming in at the same time albeit with different dates but different doses and that's a frequent query.

What are the risks if patients are not educated?

There are the obvious risks. Patients' adherence depends on physical and perceptual ability to take the drugs. From the perceptual side of things they have to understand what the immuno-suppressants are for, what the benefits are and the impact if they stop taking it. They also have to be confident that these drugs aren't going to do significant harm. Often we see patients who don't want to take them because they think it'll cause cancer or something and clearly you talk about the risks but you've got to educate them on the whole risk benefit analysis. The patients have access to the drugs as well so they've got to be able to have either a supply home with them that reflects the prescription they've been given. A classic example is discharge on prograf 5 mg twice a day and when they come to the first clinic appointment, the dose needs to go down to 4,5 mg and suddenly they need 1,5 rather than the 5's and they don't have the right tablets and the delay in getting the correct tablets from a pharmacy is too long so it is physical reasons and perceptual reasons why they may not be able to take the tablets like they're meant to.

Who educates the patient and is there a record of this?

There's a formal self medication programme which is documented. I have some concerns that it is not. It's like many of these check lists; you can tick boxes, but it doesn't necessarily mean that things are actually happening as you think they are. We see patients who have passed through the self med programme, and come and clearly don't understand and I think that comes back to what I was saying with individual patients' need to be treated in different ways but the education continues and we reiterate a lot of the purpose and function and reasons behind the immuno-suppressants when they come to the clinic and that's not formally documented but it happens.

Is the patient given any written information?

Yes the patient should both have the little green book with has the lists of tablets in it and they should also have a copy of their discharge script

4. How important do you think patient adherence to drug regimen (compliance) is in this group of patients?

Critical, very important.

5. Do you think most transplant patients do adhere to their drug regimens? If not, why do you think that is?

Yes I think they do. That's probably credit to the education they do get. Most patients that leave hospital I expect don't adhere very well, but the transplant population do have that extra education. Certainly when we monitor the CNI levels, they've gone down as we would wish. On the whole I think patient adherence is very good and patients are anxious enough about it that they will phone us up and ask. In the early days, on the whole they're good, but there are clearly patients who months or years down the line who start to fall by the waste side and it's not just adhering with drug regimes, it's tending follow up clinic visits. Many aspects of the care and these are often patients we don't see because they don't come to the clinic, and they are a worry and they lose their graft.

Prescribing

1. What do you think the risks are in the prescribing of immuno-suppressants to transplant patients?

Overall under prescribing and over prescribing. You're inducing potential CNI toxicity, graft dysfunction, opportunist infection. Under prescribing you're running the risk of potential rejection. The prescribing is dependent on a number of factors; measured drug levels, graft function, timing of blood tests: we interpret blood tests as being a 12 h trough and often we say to patients what time did you take your tablets last night and you've seen them in clinic and you have to accept and recognise that the 12 h through actually is a 10,5 h or 14 h level. It may not fit exactly and you have to take a bit of a guess and there may be other things like the patients has got diarrhea and that increases tacro (tacrolimus) absorption so you can have levels that are not reflecting what you hoped they would.

2. Monitoring is important in the use of immuno-suppressants, and blood tests are taken frequently. How are the results of the blood tests taken into consideration at the time of prescribing?

Very much so. Patients that have been to clinic this morning, I'll get their blood results and usually 80 % of the time, I'll get their tacrolimus levels back this evening and if they need a dose change, I will phone them this evening so we don't change the dose until we have a measure.

3. Who (which grade of doctors) does most of the prescribing of immuno-suppressants on the ward?

As inpatients in the ward: predominantly consultants because there's a daily ward round and then when the bloods including the drug levels come back in the evening there's usually a consultant who touches base with the SHO or registrar and they'll go through any changes in the drugs. But it's certainly minimum registrar level.

4. How important do you think it is that the GP is well informed about what happens in the clinic and hospital?

Very important, because in effect they're the ones doing the prescribing. That is also a source of problem having to convey information to the GP, and that prescription then has to go to pharmacy, and pharmacy then have to dispense the medication and each of those steps induces delay and potential error. I think GPs get anxious about it 'cause it's not something that they are handling very often and also they get quite anxious about the rapid dose change because it's something that their systems don't cope well with. After each clinic visit a letter is generated. Initially it's 3 times a week and by the time the letter gets to the GP they might be confronted with two letters with different doses.

What are your perceptions of consequences if the GP is not being informed?

Patients don't get the right dose. Patients find it frustrating, they go to the GP and GPs aren't happy to prescribe the drugs so they'll often end up coming back to us and asking for a hospital prescription so it's a number of adverse consequences. The kind of thing that really helps is if we see a patient, and the letter is dictated and the letter is typed ideally tomorrow, they're out quickly, but if there's a problem with secretarial staff it can be ten days before the letter is done and by then the patient may have been seen 2-3 more times so I think what really helps is if the patient are well informed and they have access to a range of tablets sizes then you can actually do those dose adjustments without it having to go directly through the GP and the GP could then just be informed of the changing dose. I think it's really problematic if you're having to wait for the patient to go to the GP. It can't work that way, so the patients needs to have access to a range of different tablets so that they can make a dose change immediately tonight reflecting a high level this evening or something like that, and not wait for GP next week.

5. In your opinion, what information needs to be provided to the GP?

Contemporaneous, up to date list of medications

6. What information is provided to the GP about current drug regimen at discharge, and eventual changes in drug regimen and how is this documented?

They get a copy of the discharge letter which is given to the patient and GP and other relevant medical staff. That's then followed up quite rapidly in transplant patients with an early clinic review. The clinic letters with all have copies of the drugs from proton.

7. At the time of prescribing, do you think drug interactions are taken into consideration?

Yes I would hope so. There are going to be occasional ones that will be missed but the important ones like diltiazem, quinolone antibiotics, antifungals etc are always considered

8. Would you consider drug interactions to be an important issue in the administration and prescribing of immuno-suppressants?

Yes they are but if you've got a patient who is on a regular dose of diltiazem, then you just need to adjust the prescribing dose. It's a safe and constant interaction therefore you run with it. It doesn't stop you from prescribing, but you just need to factor it in your initial dosing.

9. If at a point in time, the prescribing doctor is uncertain about anything regarding prescribing of the drug, what action do you think the doctor will take?

I would hope that they would look up or seek further information from other people, books etc.

Participant 7; senior doctor

Administration

1. What do you think are high risk areas in the administration of immunosuppressant medication in transplant patients? (That is, are there any particular steps in the medicines administration process where you think things are likely to or could go wrong?)

I think in the early periods the dangers with immuno-suppressants are infection, our own experience the problems have tended to be in the first couple of months when we've given MMF and high dose CNI particularly in people who have been re-transplanted because of an immune mediated liver injury. I think we've run into one or two infective problems at that time and one or two bad CMV's in that situation and pneumocysts as well. In terms of long term effects the major problems we've seen have been with renal dysfunction and with malignancy. I think now we probably reduce immuno-suppressants more appropriately as time goes on: When people are 3-4 years out, we quite happy to run with just Tacrolimus at a level of 3-4 and we're more likely to stop AZA or other agents as time goes on. In terms of the people who need more immuno-suppression..the younger who've had rejection episodes, I think we use more MMF now and we have also started to use combinations involving sirolimus where the CNI are limited because of the renal toxicity so we can't give big doses of CNI into the patients, we've used in a number of patients now sirolimus in combination with either tacrolimus or cyclosporine. I'm not sure if that's going to be of benefit in the longer term but certainly for the one or two patients we've struggled and they've lost grafts from immune injury they seem to be working relatively well in combination. It is a very immuno-suppressive combination. I can remember one slightly older patient that we gave that combination to that ended up with severe infective problems because of the immuno-suppressants.

2. The nurses have a lot of responsibility and are busy around the ward. What impact do you think this could have on drug administration to patients?

Do you think procedures are always followed?

I think probably 90 % of the time they do get their meds on time but hospitals being busy places and people being sick from time to time there will be a slight deviation in the time given. But on the whole I think they do.

3. After being discharged, do you think the patients go home with enough knowledge to safely take their immuno-suppressants in the way they were intended?

I think there's probably 3 sorts of patients. There are people who are very keen on knowing all about their meds, and what it's for and they're very regimented in taking it. They ask questions, and read up and want to know more. There are people who don't really want to know anything but are quite specific in obeying orders. They understand that they have to take their meds and they'll stick to what they're told but don't really understand that much about what they're for, but they know that they're important and that's all that matters to them. And then there are people who kind of fall in between who know a little bit and know that they're important but aren't that vigilant in taking their meds in terms of their adherence to the prescription. In my experience they tend to be the younger people who are a bit too interested in other things than taking care of their health.

What are the risks if patients are not educated?

Graft loss if they don't take their meds for a prolonged amount of time. I think everybody tries to stress to them the importance of doing that, until they physically feel either sickness or are faced with the stark realisation that their livers not working. I think that's a wake-up call. Up until that point I think you can educate them and tell them as much as you want and it don't think it's going to make that much of a difference.

Who educates the patient and is there a record of this?

There are different phases of self medication and there is a record they go through. It's done by the nurses and then the pharmacists make sure that they know what the tablets are.

Are they given any written information?

Yes they are. I've seen the sheets.

4. How important do you think patient adherence to drug regimen (compliance) is in this group of patients?

I think liver transplant is one of the more important areas of taking medication. If you miss the odd tablets here and there but if you miss the immuno-suppressant or prophylaxis like valganciclovir that can be very important. It is an important group of patients that are reasonable regular in taking their medication.

5. Do you think most transplant patients do adhere to their drug regimens? If not, why do you think that is?

It depends on how you define adherence. If you mean adherence 90 % of the time they take their tablets around 1 hour around when they're suppose to, I'd say yes. If your adherence is strict I'd say no.

Prescribing

1. What do you think the risks are in the prescribing of immuno-suppressants to transplant patients?

The risks are different formulations of the same drug. MMF which is cellcept which is 500 and then there's MMF myfortic which is a different dose. There is tacrolimus in the form of prograf and advagraf and now generic. Cyclosporine is neoral and generic as well. So there are issues with the formulation of the same medicine and there are also issues when you switch from one immuno-suppressant to another, because tacrolimus prograf is twice a day and if you switch to something like sirolimus which is once a day and we've had issues with people taking sirolimus twice a day because they thought it was a direct change from tacrolimus. The other issue that we've had has been people taking 5 mg instead of 0,5 mg of tacrolimus and also 5 times 5 mg, because you get prograf 1 mg tablets or 5 mg tablets and we had someone who took five 5 mg tablets so 25 mg and he got into major problems so I think there are issues in the dose itself, there are issues in the different formulations, and there are major issues when you switch from one immuno-suppressant to another, and the only way really that you get round that is by going over with the patient and writing it down in clinic, you have to go over that it's not suppose to be taken twice a day and make sure they understand that. Most of the time it works but in the occasional patient there is a problem.

2. Monitoring is important in the use of immuno-suppressants, and blood tests are taken frequently. How are the results of the blood tests taken into consideration at the time of prescribing?

Monitoring for trough levels is really only done with the CNI and sirolimus. We get the results of the troughs of the CNI either the day of the tests or day after, sirolimus takes some time because it is sent away. So we look at the tests and if they are in-patients we modify the dose for the next day, if they're out patients then we have a follow-up meeting 2-3days after clinic, and if there is to be a change in dose it is written on the follow-up sheet and the co-coordinator phones the patient to tell them of the change in dose so that doses are changed either by telephone by co-coordinator or by a change in the prescription on the ward.

3. Who (which grade of doctors) does most of the prescribing of immuno-suppressants on the ward?

The signing of the prescription is either done by the registrar or the junior doctor below, the foundation doctor, the (noise) and it is usually at the ward round at the instruction of the consultant physician. At the meeting on the ward round, we would discuss if there's a change

and if the discussion isn't there then it's usually at the bedside by the patients where we look at levels and decide. But the actual prescription is usually signed by one of the junior doctors.

4. How important do you think it is that the GP is well informed about what happens in the clinic and hospital?

Extremely important. One of the major difficulties we've had in recent months and years is correspondence with the GP because typing and issues around discharge and clinic letters go behind. The patient hopefully know what they're taking, and there was a written document in the notes but there was no dictated letter to the GP so quite often the GP would be a few weeks behind what was physically happening. That can be a problem if the patient goes for a repeat prescription particularly if there's a change. If it's a switch then it's even worse because they're not aware. We've had issues with that and I think we can probably be better at that. How will we do it I'm not entirely sure unless the patient had it in their book and they took it with them and it was signed.

What are your perceptions of consequences if the GP is not being informed?

We've not had any major consequences it just means a lot of running around for the GP as well. They will often phone and say that the patients tells me that the does have changed, can you fax me something to confirm this. I don't think it's translated into major problems in terms of treatment, I just think it's translated into problems for the time wasting for GP chasing us around.

5. In your opinion, what information needs to be provided to the GP?

Transplant is fairly specialized and I don't think the GP will want to know particularly why we've changed doses etc. I just think they need to know the prescription and the dose. I think if there's a switch in medication, there needs to be some explanation to why the switch has taken place as well as the dose that is used, whether that dose will change in time of whether it's a fixed dose forever. So I think they'd like to know if it's likely to change and over what sort of time period.

6. What information is provided to the GP about current drug regimen at discharge, and eventual changes in drug regimen and how is this documented?

Usually the clinic letters the present dose is given and if there is any changes it is given there as well. I'm not sure of what everybody's practice is in terms of saying that a lot of drugs are going to be stopped at 3 months and altered. I usually say that at 3 months there will be significant changes and after that most people only remain on tacrolimus, CNI and AZA or MMF after that. I'm not sure if there is any other formal information that is given to GP. This is documented through clinic letters.

7. At the time of prescribing, do you think drug interactions are taken into consideration?

I think they're taken into consideration. They might not always be known. From the GPs point of view, they are reasonable good at calling us if they have a concern or if they're starting new meds. It's quite regular for them to phone and ask "is it ok if we give this?". But we've been called out a few times particularly with antibiotics like clarithromycin or something like that where that hasn't been discussed with us and they've been put on it. Not just by GPs but by other hospitals. So I think within the unit we're reasonable good, but as a whole it probably could be better..

8. Would you consider drug interactions to be an important issue in the administration and prescribing of immuno-suppressants?

Yes

9. If at a point in time, the prescribing doctor is uncertain about anything regarding prescribing of the drug, what action do you think the doctor will take?

Speak to Kat. We do that quite regularly. We value certainly the pharmacists and they're quite rigorous at looking at things up so if we're uncertain I usually just speak to Kat.

Participant 8; Transplant ward pharmacist

Administration

1. What do you think are high risk areas in the administration of immunosuppressant medication in transplant patients? (That is, are there any particular steps in the medicines administration process where you think things are likely to or could go wrong?)

I'd say high risk..it's probably in the prescribing..Oh sorry administration. So, there's the pressure that the nurses are under on the ward I guess. Drug rounds and not being distracted from that. And also with the tacrolimus with the different brands.

2. The nurses have a lot of responsibility and are busy around the ward. What impact do you think this could have on drug administration to patients?

It certainly could have a negative impact 'cause there is a lot of pressure on them to do lots of different things as well as the drugs so ehm that can be detrimental.

Do you think procedures are always followed?

Laughs. Probably not but I don't think that's specific to transplant. I think you'll find any ward in this hospital is probably taking work-arounds or short-cuts or whatever.

3. After being discharged, do you think the patients go home with enough knowledge to safely take their immuno-suppressants in the way they were intended?

I may be quite bias because I like to think that they do because I make the point of speaking to patients. But I know that the nursing staff will spend some time with the patients and with the

liver patients, I will speak to them all about their new medicines and there's also a little section in the liver transplant-going home book. I think there's similar for renal as well so they probably do but maybe that could be improved on.

What are the risks if patients are not educated?

They just don't understand what they're taking, why they're taking it and they take it incorrectly

Who educates the patient and is there a record of this?

I speak to them but I don't actually record it which is probably something I should make a point of writing in the notes that I have done so.

Do you know if there is any written information given to the patient?

Yeah, they all get the standard information-sheets about each of the individual medicines-

4. How important do you think patient adherence to drug regimen (compliance) is in this group of patients?

Obviously it is vital to the success of the graft.

5. Do you think most transplant patients do adhere to their drug regimens? If not, why do you think that is?

Yeah probably. There's probably..with the younger sets of patients, they maybe not taking their twice daily tacrolimus, they maybe not taking their evening dose but I suppose the other side to that is what's the significance of that.

Prescribing;

1. What do you think the risks are in the prescribing of immuno-suppressants to transplant patients?

The risks would be 'cause they could be toxic medicines, potentially toxic, just a lack of understanding of what's being prescribed.

2. Monitoring is important in the use of immuno-suppressants, and blood tests are taken frequently. How are the results of the blood tests taken into consideration at the time of prescribing?

Well for in-patients the bloods are reviewed every day and are then used when making decisions. For out-patients for liver anyway their bloods are reviewed together with the co-ordinator and the doctor from that clinic and any changes made are communicated to the patients. So they are in my experience always used closely.

3. Who (which grade of doctors) does most of the prescribing of immuno-suppressants on the ward?

Ehm..I would say 50/50 split between the registrar and the junior doctor but the registrar would probably be always prescribing the calcineurin inhibitor, the tacrolimus and that would always be with the consultant looking over their shoulder. Years ago it was only the consultant that wrote that prescription but that's not been like that for a while. But it is very closely looked at.

4. How important do you think it is that the GP is well informed about what happens in the clinic and hospital?

Yeah it is very important but I appreciate it can be quite tricky 'cause some patients are changing a lot and obviously the specialist knowledge is here so it's keeping that information up to date with the GP can be difficult.

What are your perceptions of consequences if the GP is not being informed?

Well I guess..ehm...in terms of just making sure that their record is up to date and then the patient..does he know what he's taking because he's getting different stories between hospital or GP and if the GP starts any new medicines, are there interactions, all the information available for interactions and that type of thing.

5. In your opinion, what information needs to be provided to the GP?

Ehm. In terms of drugs? Just doses, formulations, the brand, the importance of brand prescribing. For tacro and cyclosporine, the current dose and any... I suppose it is tricky because a lot of it is managed here in the hospital, they'll be taking the steroids down and that'll be up to them. Patients are individuals. You can't just say to the GP in two weeks we're going to reduce the prednisolone, because we don't know what's going to happen in two weeks. Just making sure the GP has an idea if what will be.. should be happening.

6. What information is provided to the GP about current drug regimen at discharge, and eventual changes in drug regimen and how is this documented?

So when the patient is discharged, they get an immediate discharge letter. A copy of which goes to the GP. The patients themselves should also have the green book which you know..that's more for the patient and then what's meant to happen is a much more full discharge summary is typed dictated by the registrar which has details about all the operation and any other things and that has the meds on it. The shared care protocols are available online. We used to send out paper copies but just to keep it future proof, they're available online and GPs should be able to access them. Of course the other issue is that we're a national unit and shared care protocols only really apply in Lothian.

7. At the time of prescribing, do you think drug interactions are taken into consideration?

Yes

8. Would you consider drug interactions to be an important issue in the administration and prescribing of immuno-suppressants?

Yes (laughs)

9. If at a point in time, the prescribing doctor is uncertain about anything regarding prescribing of the drug, what action do you think the doctor will take?

I think if it's one of the juniors they'll speak to the reg (registrar) or a consultant and then they'll speak to pharmacy as well. In terms of interactions they're pretty good at referring back to us.

Participant 9: Junior doctor

Administration

1. What do you think are high risk areas in the administration of immunosuppressant medication in transplant patients? (That is, are there any particular steps in the medicines administration process where you think things are likely to or could go wrong?)

Ehm..I guess you could be giving the wrong dose and you'd be giving the wrong medication. Most of our patients are on Tacrolimus, and sometimes there's the occasional patient on cyclosporine so that can get mixed up. Ehm..and some patients are on twice daily prescriptions whereas other people are on once daily so there could be mistake made with that. And I guess as for all drugs things can be given to the wrong person and prescriptions can be written incorrectly.

2. The nurses have a lot of responsibility and are busy around the ward. What impact do you think this could have on drug administration to patients?

I guess if they're busy they don't necessarily take as much care with things and if they're rushed and having to do different bits and pieces then things can be missed or given incorrectly.

10. Do you think procedures are always followed?

I've only worked here for a week. From my experience the procedures seem to be quite well followed.

3. After being discharged, do you think the patients go home with enough knowledge to safely take their immuno-suppressants in the way they were intended?

I don't know what...I'm not entirely sure what kind of education they get. Certainly from us they probably don't get very much information about safely taking their medication. I think most of that information comes from the pharmacist. We probably don't tell them anything at all really other than what dose to take so from my point of view we don't give them enough information.

What are the risks if patients are not educated?

Well they're quite dangerous drugs. Drugs that have got quite a few side effects that can potentially be very serious. So if they take them incorrectly because they don't know the potential for these side effects. They don't know how to take them then that's potentially more hospital admissions or you know worse outcomes for the patient. And if they don't take them at all or take as much as they should then there's a possibility of rejection of their organ as well which is kind of a waste of what they've been through.

Who educates the patient and is there a record of this?

I don't know but I assume that the pharmacist and I imagine the transplant co-ordinators probably have a bit to do with it as well. I don't know where the record of that would be. I've never seen a record of education. I hope it happens! I just assumed that it did.

Do you know if there is any written information given to the patient?

I don't know.

4. How important do you think patient adherence to drug regimen (compliance) is in this group of patients?

Oh I think it's really important. 'Cause the consequences of them taking their medication incorrectly or not taking their medication are so serious that it's really important that they do take it correctly and we have had people in who don't...who are not taking their medication properly who've had to come back into hospital..so the consequences of not doing it properly is serious.

5. Do you think most transplant patients do adhere to their drug regimens? If not, why do you think that is?

Ehm..I don't know. I assume..I think probably the ones we get back into hospital are the ones that don't comply so I don't really see the people who get on with it. It's probably difficult..It's difficult enough to take any medication but for something particularly immuno-suppressants that have to be taken at the same time, have to have levels and things done, that's probably more difficult to take than a lot of normal kind of drugs. I'm sure there are people out there who aren't it as they're prescribed but I don't necessarily see them so I don't know how common it is.

Prescribing;

1. What do you think the risks are in the prescribing of immuno-suppressants to transplant patients?

Well for me, I don't have very much experience in it 'cause I just started this job so I think the risks are that people who don't have experience in it are prescribing medications and we ask for advice from the senior doctors about it and we always discuss what's going on but sometimes, occasionally people get missed out on the ward round or whatever and their immuno-suppressants don't get prescribed then. And then later on maybe over night, they

realise that they've not been prescribed and doctors coming on who don't know patients, don't know the drugs, don't know what their levels are, and they're prescribing medication. So I think sometimes things get missed a bit, but I think asking advice from senior doctors and pharmacist is the best way not to cause any harm, hopefully!

2. Monitoring is important in the use of immuno-suppressants, and blood tests are taken frequently. How are the results of the blood tests taken into consideration at the time of prescribing?

So we do blood tests on Monday, Wednesday and Friday for the immuno-suppressants here and then we'd look at the test results before we'd prescribe the following days' immuno-suppression. But like last week there was a problem in the lab and we didn't get any levels or between Monday and Friday, the Wednesday set, went didn't get any levels at all. So we were a bit kind of blindly prescribing there so I guess that's one of the dangers; you're relying on the lab to work and us to get the results back in time to prescribe it.

3. Who (which grade of doctors) does most of the prescribing of immuno-suppressants on the ward?

Oh it'll be me. So I'm an FY2. I think I probably do most of the actual prescribing. Most of the time I do what I've been told to do or making adjustments that have been discussed with other people for any kind of immuno-suppression or any other kind of medications. But in terms of actually prescribing it, it's usually me.

4. How important do you think it is that the GP is well informed about what happens in the clinic and hospital?

I think it's really important because the GPs are kind of an everyday link with the patients. The patients can see them kind of in between clinics and things and if they don't know how much the patient is meant to be taking then that can cause all sorts of confusion and then they might need to contact the hospital to find out how much they should be on. And then the GP is probably quite useful to monitor that they're actually taking the medications so I think there needs to be quite good communication with the hospital, the out-patient clinic and the hospital to make sure everyone knows what's going on. And it's quite scary when you're a GP to deal with patients that are transplant patients because they're so special and all the drugs are odd and not stuff that you deal with all the time so I think it's important to let the GPs know as much as you can so that they've got a better idea of what's happened and how much medication they're on.

What are your perceptions of consequences if the GP is not being informed?

Well if the patient is ill with another problem. If they've got an infection or something then it's important that the GP knows about their immuno-suppression and how much immuno-suppression they're on. I think they need to know kind of what they've already been taking and especially with interactions as well with other medications if they want to prescribe

something else. So I think lots of things could go wrong if they weren't informed of the medication.

5. In your opinion, what information needs to be provided to the GP?

From an out-patient clinic I think they need to know exactly what medication they're on and what times the patient should be taking them and what dose they're taking at the minute and the arrangements for the monitoring. I'm not sure whether it gets done. I presume it gets done in between by the GPs or maybe it gets done just in the clinic..I don't know 'cause I've not been in clinic but it'd be important to know what monitoring there's going to be and they probably need to know a contact to get in touch with if there are any problems with it so that they've got someone to ask questions to 'cause like I said it's not something that you'd (noise) everyday.

6. What information is provided to the GP about current drug regimen at discharge, and eventual changes in drug regimen and how is this documented?

So at discharge we send out an immediate discharge letter with the patient. I don't know if you've seen them but it has a list of patients medication on it and it should have..it has a space in the letter to write if there's been any changes to medication. So you should put there's been dose changes and things like that on it, and there's also a bit in the letter that says any other information that the GP should know. So that's where you could add in important things to look out for, what interactions they need to worry about but probably... I haven't written any myself for patients who've just had transplants. I'd probably want to give the GP a quick call and let them know what's been happening as well 'cause they probably have one patient over their 50-year career that has had a transplant so it'll be entirely new to them. I quite like to give people just a call and let them know that this patient is getting out of the hospital and that they're on these strange medications.

7. At the time of prescribing, do you think drug interactions are taken into consideration?

I think if they're on a ward round with a pharmacist yes, but if not probably not enough. I'm not aware of all of the interactions of all of the medications and if there's anything I'm worried about I'd look it up in the BNF or give the pharmacist a call. But probably not enough thought about..interactions.

8. Would you consider drug interactions to be an important issue in the administration and prescribing of immuno-suppressants?

Yeah, I think it probably is quite a big problem and in hospital everyone's immuno-suppressant doses changes all the time and it's probably affected by other things that we're doing and giving them and certainly I don't probably think about it. It's good to have someone going along and checking prescriptions that you do and I think it's important that we do have someone there who looks at everything but at the time I probably don't think about it.

9. If at a point in time, the prescribing doctor is uncertain about anything regarding prescribing of the drug, what action do you think the doctor will take?

Usually if there's something I'm not familiar with or not happy with I speak to the senior doctors, the pharmacist, have a look in the BNF and see if there's any kind of information in there but generally take advice of other people. And it's important not to prescribe things that you're not happy with and you're not sure of the dose or the timings or whatever. Yeah (noise). I'm sure it probably does happen but try to be as safe as you can.

Participant 10: Transplant ward pharmacist

Administration

1. What do you think are high risk areas in the administration of immunosuppressant medication in transplant patients? (That is, are there any particular steps in the medicines administration process where you think things are likely to or could go wrong?)

I think one of the biggest areas...it's a very specialist area. That's one of the drawbacks that there can be risks with a specialist area and those drugs are not used elsewhere so the people that are there, they'd have to have that specialist knowledge about how to prescribe and administer those medicines and that is a risk because then, they need to be appropriately aware of those medicines and they won't come across those medicines anywhere else so it's a very select few that know about them.

2. The nurses have a lot of responsibility and are busy around the ward. What impact do you think this could have on drug administration to patients?

If they are busy then they might get interrupted and doing various things as answering the phone and being interrupted by another member of staff. That is risky because you know they're in the middle of something getting interrupted and that is a risk as well because they come back to it and they might think they've done something but haven't or the other way around. As well, if they're really busy, they might pass a message on to someone else for something and that message might not get across to the appropriate person so there might be a risk in that as well if there's not the right person to speak to at that point.

Do you think procedures are always followed?

No I don't think so.

3. After being discharged, do you think the patients go home with enough knowledge to safely take their immuno-suppressants in the way they were intended?

It's very varied. It depends on the length of stay they've had, what information they've received from the various team. Some might get discharged before speaking to a pharmacist if it's the weekend or evening or due to the pharmacist not being around on the ward, not being present, not being able to speak to them, so they might get missed. The co-ordinators also speak to the patients but they might not have been spoken to at that point, so it just depends

on what information they've had from various people and what information they've had from nursing staff as well. There's no way to say that every patient will have the same level of input.

What are the risks if patients are not educated?

They might not know how to take their medicines appropriately and that has great implications in terms of them not losing the function of their organ, not complying with medicines, they might not know why they've been prescribed something, they might not think it's important so they might miss it, and they might take double of something 'cause they're not sure about medicines so there's always that risk that they've not sure how to take them appropriately.

Who educates the patient and is there a record of this?

There's no record other than our official...our screening sheets that we have within pharmacy, that's just our own in-house and not an official record but we would mark down whether we have seen a patient first time or checked the kardex, we've counselled them..that's for our own records, there's nothing official to say that we've counselled a patient. It's not recorded anywhere officially.

Do you know if there is any written information given to the patient?

They are, they do the self administration scheme. When they're ready to start that they'll get informational leaflets of the drugs that they're on and that'll be placed in the folder for them to read over. They take that away with them so they have a sheet for each drug and they get a green booklet as well which has got a bit of information and monitoring what medicines they're on, recording what they're on. They take that to clinic with them as well to get it updated.

4. How important do you think patient adherence to drug regimen (compliance) is in this group of patients?

Very important. The consequences are that they might lose their graft.

5. Do you think most transplant patients do adhere to their drug regimens? If not, why do you think that is?

I think most of them do. I'd say the majority of them do but there's always people that don't like taking medicines for whatever reason. And maybe as you get further down the line they might become less compliant because they think they've not had any problems and they think well, if I don't take them it won't matter and they you get a bit lazy and the consequences of that so, I think most of them so realize how important they are.

Prescribing;

- 1 What do you think the risks are in the prescribing of immuno-suppressants to transplant patients?

Again it's a very specialist group of patients, a select few drugs so the risks are that there's lots of different staff members rotating so they might lose knowledge about prescribing when they go elsewhere, and they then come back and are not used to prescribing that. So that's a risk and as I said it's a select few drugs so they won't use these drugs elsewhere so that's a risk as well. They're quite specialised.

- 2 Monitoring is important in the use of immuno-suppressants, and blood tests are taken frequently. How are the results of the blood tests taken into consideration at the time of prescribing?

Well we currently do daily meetings in the morning where we will review and discuss patients' blood results in the morning so all patient results that are in in-patients will be discussed by the transplant team in the morning and everyone is free to attend that meeting and the pharmacist usually attends, the appropriate junior doctor, the consultant and his team will attend that ward round. So the results are reviewed daily and then it's a walk around ward round so the results are taken into consideration when they're prescribed.

- 3 Who (which grade of doctors) does most of the prescribing of immuno-suppressants on the ward?

I would say the registrar and the SHO.

- 4 How important do you think it is that the GP is well informed about what happens in the clinic and hospital?

Very important because they need to keep their records up to date and they need to know what the patient is on and what changes 'cause they might be following up those changes to they need to know if any changes have been made.

What are your perceptions of consequences if the GP is not being informed?

Quite often they might be on medicines and we might start something else and the GP might continue prescribing something that might not be appropriate with the new medicines and if they're not aware of it, it can be a risk. So they might start therapy (noise) (...) not aware of so they need to know what is being changed.

- 5 In your opinion, what information needs to be provided to the GP?

A concise written information of what the patient is being discharged on and maybe a summary of pre-medicines that have been discontinued or changed but a concise summary of what they're being discharged on, yes so they can update their records.

6 What information is provided to the GP about current drug regimen at discharge, and eventual changes in drug regimen and how is this documented?

At discharge they will get a copy of the discharge script listing their current medications and a brief summary of the discharge letter..that'll go to the GPs. It's documented through the discharge letters; one copy goes to the GP, one to the patient and one is filed in the patients' notes.

7 At the time of prescribing, do you think drug interactions are taken into consideration?

Sometimes as it depends on the experience of the prescriber and whether there's the presence of a pharmacist and their experience in that area.

8 Would you consider drug interactions to be an important issue in the administration and prescribing of immuno-suppressants?

Absolutely yes, because there's a lot of interactions with say tacrolimus which we use commonly so yeah.

9 If at a point in time, the prescribing doctor is uncertain about anything regarding prescribing of the drug, what action do you think the doctor will take?

They would usually maybe ask their senior or ask the pharmacist if they get hold..they will try and contact you as the pharmacist.

Appendix 6: Questionnaire

Questions for interviews with staff

Administration

1. What do you think are high risk areas in the administration of immunosuppressant medication in transplant patients? (That is, are there any particular steps in the medicines administration process where you think things are likely to or could go wrong?)
2. The nurses have a lot of responsibility and are busy around the ward. What impact do you think this could have on drug administration to patients?

Do you think procedures are always followed?

3. After being discharged, do you think the patients go home with enough knowledge to safely take their immuno-suppressants in the way they were intended?

What are the risks if patients are not educated? Who educates the patient and is there a record of this?

Do you know if there is any written information given to the patient?

4. How important do you think patient adherence to drug regimen (compliance) is in this group of patients?
5. Do you think most transplant patients do adhere to their drug regimens? If not, why do you think that is?

Prescribing;

1. What do you think the risks are in the prescribing of immuno-suppressants to transplant patients?
2. Monitoring is important in the use of immuno-suppressants, and blood tests are taken frequently. How are the results of the blood tests taken into consideration at the time of prescribing?
3. Who (which grade of doctors) does most of the prescribing of immuno-suppressants on the ward?
4. How important do you think it is that the GP is well informed about what happens in the clinic and hospital? What are your perceptions of consequences if the GP is not being informed?
5. In your opinion, what information needs to be provided to the GP?
6. What information is provided to the GP about current drug regimen at discharge, and eventual changes in drug regimen and how is this documented?
7. At the time of prescribing, do you think drug interactions are taken into consideration?

8. Would you consider drug interactions to be an important issue in the administration and prescribing of immuno-suppressants?
9. If at a point in time, the prescribing doctor is uncertain about anything regarding prescribing of the drug, what action do you think the doctor will take?

**Appendix 7: Care issues encountered most frequently by
pharmacist at the transplant ward**

Care issues encountered by pharmacists

The pharmacists on the transplant ward were asked to list the care issues that were encountered most frequently. The main topics that came up were that they were involved in the education of patients before discharge and that they felt they helped identify interactions of immuno-suppressants with non-immuno-suppressant related drugs. This was because the specialist staff might not know about the interactions with drugs outside their field.

Appendix 8: Pharmacist check-list

Pharmacist check-list		1	2	3	4	5	6	7	8	9	10
Initials											
Ward:											
type of transplant											
Number of days since transplant:											
Pharmacist:											
1 Unnecessary drug therapy	a) There is no valid medical indication for the drug therapy at this time										
	b) Multiple drug products are being used for a condition that requires fewer drug therapies										
	c) Drug therapy is being taken to treat an avoidable adverse reaction associated with another medication										
	d) The duration of therapy is too long										
2 Need for additional drug therapy	a) A medical condition requires the initiation of drug therapy										
	b) Preventive drug therapy is required to reduce the risk of developing a new condition										
	c) A medical condition requires additional pharmacotherapy to attain synergistic or additive effects										
	d) The duration of drug therapy is too short to produce the desired response										
3 Ineffective drug	a) The drug is not the most effective for the medical problem										

	b) The formulation of the drug is inappropriate																			
	c) The drug is not effective for the indication being treated																			
	d) The dosing interval is incorrect																			
	f) Route of administration is incorrect																			
4 Dosage too low	a) The dose is too low to produce the desired response																			
	b) The dosage interval is too infrequent to produce the desired response																			
	c) A drug-drug/food/lab/disease interaction reduces the amount of active drug available																			
5 Adverse drug reaction	a) The drug product causes an undesirable reaction that is not dose-related																			
	b) A safer drug product is required due to risk factors																			
	c) A pharmacodynamic drug-drug/food/lab/disease interaction causes an undesirable reaction																			
	d) The dosage regimen was changed too rapidly																			
	e) The drug product causes an allergic reaction																			
	f) The drug product is contraindicated																			
6 Dosage too high	a) Dose is too high																			
	b) The dosing frequency is too short																			
	c) A drug-drug/food/lab/disease interaction occurs resulting in a toxic reaction to the drug product																			
	d) The dose of the drug was administered too rapidly																			

7 Inappropriate compliance	a) The patient prefers not to take the medication												
	b) The patient forgets to take the medication												
	c) The patient cannot swallow or self-administer the drug product appropriately												
	d) The time of dosing or the dosing interval is decreasing compliance.												
8 Unclassified i.e. Non-DTP	a) Formulary adherence, e.g. generic switch												

Appendix 9: Patient journey

Case study of a liver transplant patient

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Case summary

Summary of history: A 62 year old female who had a liver transplant on the 17th August 2010 was readmitted on the 8th of October 2010 because of deteriorating liver function tests (LFT) and doctors feared acute rejection. A biopsy was taken, and showed that she had microscopic abscesses syndrome. This is self limiting and requires no treatment.

Patients' diagnoses before transplant

End stage liver disease secondary to PSC (Primary Sclerosing Cholangitis). PSC is a chronic liver disease caused by inflammation and scarring of the bile ducts of the liver. The underlying cause of the inflammation is thought to be autoimmunity, and the ultimate treatment is a liver transplant.

Autoimmune cholangiopathy is a disease that represents an overlap between autoimmune hepatitis, sclerosing cholangitis and primary biliary cirrhosis.

Hepatic encephalopathy is the occurrence of confusion and altered level of consciousness as a result of liver failure. It can lead to coma. It is caused by the accumulation of toxic substances in the bloodstream that would normally be removed by the liver.

Abdominal ascites is the term used for fluid accumulation in the abdominal cavity. Its most common cause is cirrhosis, liver failure and portal hypertension.

Liver cirrhosis is the development of scar tissue that blocks the portal flow of blood through the liver and disturbs its function.

Oesophageal varices are caused by portal hypertension due to liver cirrhosis. It happens when the veins in the lower part of the oesophagus get very dilated and can lead to bleeding.

Treatment

A transplant patient of any kind will need to be on immuno-suppressant medication for the rest of their life. The body's immune system will recognise the transplanted organ as foreign and try to destroy it, and the only way to overcome this is to suppress the immune system.

The medications used to do this are powerful immuno-suppressants that can have serious side effects. The calcineurin inhibitors (tacrolimus and ciclosporin) have a narrow therapeutic index and so frequent monitoring of blood concentration and full blood count is necessary.

Optimal blood concentration is also important because a low concentration can lead to organ rejection, whilst a high concentration can lead to infections and side effects.

For liver transplant patients a combination of the following immuno-suppressants is usually prescribed[1]:

Calcineurin inhibitor (tacrolimus or ciclosporin)

Prednisolone

Mycophenolate mofetil (MMF)

Sirolimus

Azathioprine

In this case the patient was taking Tacrolimus (Prograf), MMF and Prednisolone. Tacrolimus or ciclosporin are the two main immuno-suppressants prescribed[2]. One of these will always be part of the immuno-suppressive regimen in liver transplanted patients at the RIE. In this case Tacrolimus is used. Toxicity within the recommended blood concentrations can occur. Prograf is an immediate-release formulation that is taken twice daily (morning and evening). Prograf is dosed per kg so the prescriber needs to know the weight of the patient and adjust the dose accordingly.

For the first few months after transplantation, the risk for rejection is highest and so the doses of these medications are also highest at this point. As time goes by, the doses are reduced, but the patient will always have to take immuno-suppressants. There are no specific criteria of the dose adjustments done but rather the adjustments rely on the whole clinical judgement and decision making of the prescriber. They also have to be aware of the risk for infection as they are more prone to get infections because of their low immune-system. They should avoid close contact with people who have infections.

The dose of immuno-suppressive drugs in general should reflect the risks of rejection. High risk patients include those with a previous history of rejection, younger patients, females and those transplanted for auto immune diseases.

Monitoring

The following is taken from Out Patient Protocol[3] (Appendix 3), frequency of clinic visits:

<u>TIME POST TRANSPLANT</u>	<u>FREQUENCY OF VISITS</u>
Discharge to 6 weeks	weekly - 2/52
6 weeks to 3 months	fortnightly
3 months to 6 months	monthly - 6/52
6 months to 1 year	bimonthly
After 1 year	3 to 6 monthly

At each visit the out-patient protocol describes what should be covered and the appendix also offers a memory aid for doctors. Amongst the things that need to be checked are a full blood-count, body weight, liver/kidney function and blood pressure. The out-patient protocol offers detailed description of each immuno-suppressant, what can be causes of high/low blood concentrations etc. This should minimise toxicity.

For Tacrolimus (Prograf), the BNF and SPC offers in depth detail on specific monitoring that should be done[4]. See appendix 2 for detailed description. Monitoring includes blood pressure, ECG, fasting glucose, blood count, renal and hepatic function. Patients also need to be aware of the increased risk for skin cancer and educated on how to protect themselves from the sun. This applies to MMF as well.

The frequency of blood level monitoring should be based on clinical needs[5]. Levels of tacrolimus in blood may vary a lot during diarrhea episodes so extra monitoring of tacrolimus concentrations is recommended if episodes of diarrhea occur.

MMF[6]:Full description in appendix 2. Full blood counts every week for 4 weeks then twice a month for 2 months then every month in the first year, active serious gastro-intestinal disease, delayed graft function, increased susceptibility to skin cancer, bone marrow suppression.

Prednisolone:

Monitoring of prednisolone include monitoring electrolytes as the side effects of prednisolone include sodium and water retention and potassium and calcium loss. Hypertension is also a side effect and blood pressure should be monitored. Blood glucose should also be monitored closely as prednisolone can give diabetes. Side effects of prednisolone can be minimised by using the lowest effective dose for the shortest possible amount of time. Long term monitoring also include looking out for osteoporosis, muscle loss and eye problems.

Progress

1. The patient was referred from General Practitioner (GP) to Scottish liver transplant unit (SLTU) October 2002.
2. Between October 2002 and July 2010, the patient was monitored at regular clinic visits. Her condition deteriorated from the beginning of 2010 and by summer 2010, the liver transplant was considered necessary.
3. Patient assessment was arranged at the SLTU 12th July 2010. Patients referred for assessment for liver transplant are admitted to the Unit usually for five days.

The purpose of the assessment according to that stated in the SLTU patients' handbook is to[1]:

Assess the extent of the liver disease

Ensure all other medical treatments have been considered

Assess the patients' health and fitness for transplantation

Ensure there are no reasons why transplantation could not take place

Provide information about transplant to the patient and relatives

All patients are discussed at the weekly transplant meeting and decisions take account of all the views of everyone involved from the multidisciplinary team. This meeting will decide if the patient will be transplanted and the urgency of the transplantation. In this case it was decided the patient was eligible for transplant and she was added to the transplant waiting list on 16th July 2010.

4. The patient was admitted for transplant 17th August 2010. When a liver becomes available, the transplant co-ordinator and consultant surgeon identify a suitable recipient from the waiting list. The co-ordinator contacts the patient.

The nurses meet the patient and admit her to the ward. The doctors take some blood samples.

The anaesthetist comes to make sure that the patients' level of fitness has not deteriorated since the assessment and prescribes some sleeping tablets. The consultant surgeon comes to explain everything about the surgery in detail.

The nurses help the patient get ready before going to theatre. The nurse takes the patients' blood pressure, temperature and pulse.

After surgery a daily blood sample is taken to show the function of the new liver and the concentration of anti-rejection drug in the patients' body. The average stay after liver transplant is two to three weeks but is determined by blood tests (and biopsies if there are any concerns), patient progress and graft function. The patient will be supported by a large team of staff, many of whom are present on the daily ward round. These include:

Nurses

Physicians

Surgeons

Radiologist

Anaesthetist

Transplant co-ordinators

Physiotherapist

Pharmacist

Dietitian

Occupational Therapist

Social Worker

Chaplain

5. Discharged 3rd September 2010

At discharge, the patient gets a seven day supply of medications and a letter to the GP listing them all. The GP remains the patient's first line contact for all general non-transplant related issues. Potential problems with interactions may be avoided by informing GP's and patients about immuno-suppressants and what they need to be aware of. Patients should always tell GP's and pharmacists what medications they are on whenever a new drug is introduced, even OTC-drugs. If in doubt, they should contact transplant unit. The GP needs to be informed of any alterations in regimen and also needs to be aware of the signs of rejection, infection and interactions.

6. Follow up at clinic after transplantation

Patient attends follow up at clinic after transplantation for the rest of her life. However the visits to clinic become fewer and further apart as she gets better. The visit at clinic is to monitor the function of the new liver, and detect any complications as soon as possible. The

patient and her family can also ask questions they might have. A green booklet (see self medication section of project thesis) with exact details of all medicines the patient is taking is given to the patient as the time of discharge and needs to be brought at every clinic visit and updated when changes are made.

At clinic visits, the doctor and transplant coordinator will:

- discuss current health
- check her weight & blood pressure
- examine your wound
- do a physical examination
- take blood tests to check her liver function, kidney function and blood count
- take a blood test to check her blood tacrolimus level
- check for any signs of side effects from the medication
- check for any signs of rejection or infection

From out-patient protocol for the liver transplant ward there is a memory aid (one A4 sheet) intended to help doctors remember what they need to go through with each patient at clinic visits. Clinic reviews are attended by consultant/hepatologist/medical registrar and transplant co-ordinator. Changes in therapy will be passed on via the transplant co-ordinator on behalf of SLTU by telephone and documented in case notes. Alteration in therapy will also be included on the clinic letter sent to GP and referring physician.

7. 8th October 2010 patient is admitted because of deteriorating LFT. Doctors fear acute rejection.
8. 12th October 2010 patient is discharged after biopsy is taken which shows microscopic abscesses syndrome. This is self limiting and requires no treatment.

At the point of discharge, the patient was on the following immuno-suppressants (full list of all prescribed medications is in appendix):

Discharge medication	Dose	Frequency	Type of medicine
12th October 2010			
Tacrolimus capsules (prograf)	4,5 mg	Twice daily	Calcineurin inhibitor, Immunosuppressant
Prednisolone	10 mg	morning	Steroid
Mycophenolate mofetil capsules	1000 mg	Twice daily	Antiproliferative Immunosuppressant

According to recommendations made from a study funded by The American Society of Transplantation[7] from 2009, early after transplant it is usual to have a combination of two to four immuno-suppressants including calcineurin inhibitor, an antimetabolite, sirolimus, and/or corticosteroids.

Discussion

Risks in prescribing:

-Not reducing immuno-suppressants at the correct time; immuno-suppressant medication doses are highest right after a transplant and after episodes of rejection. With time the doses should be reduced and to do this patient history and complications are taken into account.

-Monitoring is a big part of the use of immuno-suppressants. In order for monitoring to be successful, the blood tests need to get to the lab on time and the lab need to process the result on time. If this does not happen there is a risk that lab results are not taken into account at the

time of prescribing. Nurses are also dependent on doctors to prescribe immuno-suppressant in time for the patient to get it at the right time. Also, when in the clinic, the patients blood tests are assumed to be 12 h troughs, but this might not always be the case.

-Transplant patients not always admitted to transplant ward. This might mean that doctors that are not familiar with immuno-suppressants are prescribing it which is a risk. The transplant ward also has a table at the back of the kardex for immuno-suppressants. This is not always to be found in other wards. Another risk in other wards is that the patients might get prescribed something that interacts with their immuno-suppressants.

-The choice of immuno-suppressant is decided for the prescriber when the in-patient protocol for liver transplant patients is followed at RIE. To prescribe the appropriate dose however, there are a lot of things that need to be taken into consideration. For example for Tacrolimus; to maintain correct dose one needs to take into account the blood concentration, time since transplant, the history of rejection and the side effects, particularly the presence of renal impairment. This requires doctors with experience. However in the in-patient protocol there is a detailed description for immuno-suppressant drug regimens. Essentially this means, all the things are in place to minimise prescribing mistakes.

-Hand writing might be difficult to read at times. This is especially important if there are inexperienced staff who do not recognize the medication names, for example junior staff or non-specialist (bank) nurses. Bank nurses are nurses who don't work in the transplant ward long term but are asked to come whenever there are shortages of staff because of sickness etc. Also, if the prescriber does not write generic for example "tacrolimus" instead of "prograf", this can lead to serious side effects or toxicity if it is not picked up by staff before reaching the

patient as the different formulation contain different amounts of active ingredients and so can give over/under immuno-suppression.

GP communication; The following is taken from the Liver Out-Patient Protocol, chapter 4 and 5[2]):

5. ROLE OF GENERAL PRACTITIONER

5.1 The GP's assistance in post transplant follow-up care is encouraged to facilitate on-going monitoring between hospital clinic visits and will be requested on an individual basis.

5.2 The GP remains the patient's first line of medical contact for all general non transplant related health enquiries.

5.3 GPs can access the shared-care protocols on the Lothian Joint Formulary site at the following address <http://www.ljf.scot.nhs.uk/scp/index.html>

As stated above, the GP is the main contact person for non-transplant related health enquiries. That means that the patient is encouraged to go to GP's for any minor illnesses. However, many medications for minor illnesses may interact with immuno-suppressant medications, and the GP and patient need to be aware of this. Patients should always take their green booklet to pharmacist or GP when they do go, so that they have a complete updated list of all their medications for the GP to see. The GP can also access the shared care protocols from the Lothian websites.

Risks in administration:

-Patient not eating, drinking or vomiting is a risk. If this is not taken into consideration, the absorption of drugs may be altered and blood levels may change, resulting in over/under

immuno-suppression. Patient might not be able to take their medicines orally at all and might chose not to take their immuno-suppressant.

-Bank nurses are often called when specialist nurses are sick or if the ward is busy and need extra staff. Bank nurses might not be familiar with the ward, medications and patients' diseases. The immuno-suppressants are specialised medicines used mostly for transplant, and the bank nurses might not have come across them in their earlier work. This can be considered a serious risk. Transplanted patients are a complex group of patients with various co-morbidities and medications. Bank nurses and staff in general that have not worked in transplant before, should have shortened protocols to give them a brief overview of what they need to be aware of.

-Nurse administering: Doctors write in the medicine chart at what time an immuno-suppressant is intended to be administered. Sometimes the doctors don't take into consideration the normal times the nurses do their medication rounds, and so sometimes nurses have to administer medications at unusual times. On a busy ward, with hand-over (hand over is when the nursing staff change shifts ie when for example day shift staff pass on messages as to what has happened during the day to the people that arrive for evening shifts), visitors, meal times etc, the nurses might find it difficult to remember to administer medications at non-routine times. Nurses might not have enough time to go through self medication like they should if they are busy. They might forget to give immuno-suppressants or there might be a delay in giving it at the right time. This can especially be an issue when immuno-suppressants are prescribed out of normal medicine rounds.

-Self administration is the process whereby the transplanted patient receives education about their drugs and then is allowed to administer their own drugs whilst in hospital under the

supervision of staff. This includes a three step process (patients start at stage 3 and work their way to stage 1) whereby the nurses and pharmacists give the patient education and have conversations about their medications. They initially assess the patient's ability to administer drug themselves. After the initial education and assessment, the nurses and/or pharmacists have to give the patient permission for them to be allowed to administer drugs themselves under supervision of nurses in the ward setting. As the patients process through the stages, the compliance checks done by the nurses get further apart. At stage 1, there are weekly compliance checks. The patient does however sign a consent form prior to this in which they amongst other things the responsibility of the medication is theirs during stages 1 and 2. The patients also receive written information about each drug. Before discharge the patients are given a green book which includes all their medications and information about them. This is supposed to be taken to every clinic visit so it is up to date and should ideally be showed to GP's and/or community pharmacy whenever the patient visits them. If this is not done the green book might include errors. Another risk might be that not all patients use the green book at all.

Self medication is for the most part a very good idea as patients get used to their drugs and it eases the fear of going home and doing everything themselves. Understanding their own drugs and how important it is to take them, might well be the key to compliance in transplanted patients. However if the patients don't receive good education and are administering the drugs themselves without fully understanding, it might be doing more harm than good. The education each patient receives might not always be satisfactory. For example if a nurse is busy or the patient is discharged at a time when the transplant ward pharmacist is not at work (evening), then the patient might not receive all the education he/she should. They might be going home with less knowledge than was hoped without being aware of this themselves.

-Compliance: There is always a risk that patients will not take their medicines. In this case it might be that the patient gets confused because there are so many immuno-suppressants (polypharmacy), the costs are high and she might forget to renew prescriptions. Some transplanted patients also think that as long as they feel well, the immuno-suppressants might not be that important to take. They might also be afraid of the side effects. Also in the time before transplant, the patient might be confused because of the nature of the disease; hepatic encephalopathy is the occurrence of confusion and altered level of consciousness as a result of liver failure. Another risk is that patients rely on family to do all their medicines and these patients might not actually understand much themselves. There is also a tendency for younger patients to care less about their compliance as they are busy doing other things and immuno-suppressant medication don't fit into their lifestyle.

Compliance after discharge from hospital can be addressed by the nurse or doctor at the clinic when they go through the green booklet, by the pharmacist in the community setting when the patient picks up prescriptions, or by the GP if the patient goes frequently. This does however all rely on the green booklet being up dated at all clinic visits (which does not always happen) and the patient remembering to bring that with her.

-Clinic visits: the clinic visits are frequent after transplantation. Although they do get fewer as time passes, for some patients it might be difficult to attend them all. Some patients have to drive a long way to go to clinic, and might not be able to drive themselves. In that way they are dependent on others. The result might be that not all patients always attend their clinic visits, and this can result in the need for dose adjustments going unnoticed for longer than they should (see monitoring above for specific drugs). However, in the patient handbook for liver transplant [1]it is stated there are various ways of getting help. The transplant co-ordinators are especially helpful and if they cannot help themselves, they will find someone for the patient that can help.

Pharmaceutical care-plan		
Care issue	Action, result, further action	Comments
Tacrolimus plasma level	Keep monitoring levels frequently	Adjust levels according to blood tests to avoid rejection/ADR
High ceiling diuretics and glucocorticoids increase risk of hypokalemia, hypocalcemia, hyperglycaemia and hypernatremia	Monitor electrolytes: potassium, potassium, calcium, Glucose, Sodium, blood pressure,	Avoid cardiac arrhythmias, muscle weakness water retention etc. Prednisolone is usually discontinued after 12 weeks post transplant.
Prescribing different formulations of immunosuppressants	Different formulations may vary in bioavailability. Inform GP of this, so the follow up prescriptions do not contain any generics. Also inform the patient. An example is Tacrolimus (prograf vs advagraf) that are to be given differently	Avoid any fluctuations of plasma levels of immunosuppressants, toxicities and unnecessary side effects. Reduce risk of rejection and infection.
Compliance and education difficulties	Ensure patient fully understands the drugs in the green booklet and the importance of them.	Avoid unnecessary non-compliance due of lack of education and understanding and reduce chances of graft rejection.
Doctors orders: All medication to be continued long term	Ask doctor if all treatment is long term. It can just be that he meant that they will be re-evaluated at the follow-up in the out-patient clinic by the doctors there.	Avoid unnecessary medications, risk of adverse drug reactions and compliance difficulties. Especially aspirin as it can contribute to GI-bleed which she is already at risk of because of her age, use of predisolone and if her liver is not working properly she might not be

		able to produce clotting factors which can increase risk of bleeding further.

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Appendix

Appendix 1; Full list of medications

Discharge medication 12th October 2010	Dose	Frequency
Tacrolimus capsules (prograf)	4,5 mg	Twice daily
Fluconazole capsules	100 mg	morning
Prednisolon	10 mg	morning

Mycophenolate mofetil capsules	1000 mg	Twice daily
Co-trimoxazole	480 mg	morning
Aspirin	75 mg	morning
Valganciclovir	900 mg	morning
Omeprazole	20 mg	Twice daily
Adcal D3	1 tabl	Twice daily
Furosemide	40 mg	Twice daily
Gliclazide	40 mg	Once daily

Appendix 2:

Tacrolimus from BNF:

“Monitor blood pressure, ECG, fasting blood-glucose concentration, haematological and neurological (including visual) parameters, electrolytes, hepatic and renal function; monitor whole blood-tacrolimus trough concentration (especially during episodes of diarrhoea)—consult local treatment protocol for details; QT-interval prolongation; neurotoxicity; increased risk of infections, malignancies, and lymphoproliferative disorders; avoid excessive exposure to UV light including sunlight”

Tacrolimus from SPC[5]

”The frequency of blood level monitoring should be based on clinical needs. As Prograf is a medicinal product with low clearance, adjustments to the dosage regimen may take several days before changes in blood levels are apparent. Blood trough levels should be monitored approximately twice weekly during the early post-transplant period and then periodically during maintenance therapy. Blood trough levels of tacrolimus should also be monitored

following dose adjustment, changes in the immunosuppressive regimen, or following co-administration of substances which may alter tacrolimus whole blood concentrations.

Since levels of tacrolimus in blood may significantly change during diarrhoea episodes, extra monitoring of tacrolimus concentrations is recommended during episodes of diarrhoea.

As with other immunosuppressive agents, owing to the potential risk of malignant skin changes, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.”

MMF:

“Full blood counts every week for 4 weeks then twice a month for 2 months then every month in the first year (consider interrupting treatment if neutropenia develops); active serious gastro-intestinal disease (risk of haemorrhage, ulceration and perforation); delayed graft function; increased susceptibility to skin cancer (avoid exposure to strong sunlight); Bone marrow suppression. Patients should be warned to report immediately any signs or symptoms of bone marrow suppression e.g. infection or inexplicable bruising or bleeding

Patients receiving CellCept should be monitored for neutropenia, which may be related to CellCept itself, concomitant medications, viral infections, or some combination of these causes. Patients taking CellCept should have complete blood counts weekly during the first month, twice monthly for the second and third months of treatment, then monthly through the first year. If neutropenia develops (absolute neutrophil count $< 1.3 \times 10^3/\mu\text{l}$), it may be appropriate to interrupt or discontinue CellCept.”

Appendix 3; Abstract from the Out-patient protocol from liver transplant ward

1. AIM OF POST TRANSPLANT FOLLOW-UP

The aim of liver transplant is to restore good health, well-being and independence to recipients. However, lifelong follow-up is necessary to maximise these aims and monitor the liver graft by:

- 1.1 Monitoring graft function:
Liver function tests, other investigations as indicated, eg. Doppler ultrasound, cholangiography, liver biopsy.
Observe for disease recurrence.
- 1.2 Monitoring immunosuppression:
Blood Ciclosporin, Tacrolimus or Sirolimus concentrations.
- 1.3 Detection/treatment of complications:
including rejection, infection, vascular and biliary complications, tumour and drug-induced complications, including hypertension, diabetes, renal impairment and hyperlipidaemia.
- 1.4 Health promotion advice and support for patients and relatives from a multi-disciplinary team.

2. SCHEDULE

The usual schedule of clinic visits, which will vary according to patients' health and location, is as follows:

<u>TIME POST TRANSPLANT</u>	<u>FREQUENCY OF VISITS</u>
discharge to 6 weeks	weekly - 2/52
6 weeks to 3 months	fortnightly
3 months to 6 months	monthly - 6/52
6 months to 1 year	bimonthly
after 1 year	3 to 6 monthly

These visits will alternate between referring hospital and the transplant unit once the patient's condition is stable. The transplant unit clinic may be an outreach clinic located at the referring hospital.

3. SHARED CARE

After 6 months post-transplant, clinic visits may alternate between RIE and the recipient's referring hospital, following agreement with the referring physician. The arrangements are as follows:-

- 3.1 Secure agreement with referring physician in writing.

- 3.2 Send referring physician updated outpatient protocol and supply of shared outpatient follow-up forms to be completed and sent by fax to SLTU.
- 3.3 The completed follow-up forms will be reviewed with the patient's SLTU notes at the clinic review meeting and any suggested alteration in medication communicated to the referring physician by letter.
- 3.4 Outreach clinics, where patients are seen in their local hospital at a clinic run jointly by the referring physician and transplant unit staff ie consultant hepatologist and co-ordinator take place in Aberdeen, Dundee, North and South Glasgow, Inverness and Wishaw.

4. RESULTS AND CORRESPONDENCE FROM REFERRING PHYSICIANS AND GPs

- 4.1 The Transplant Co-ordinators are responsible for requesting and obtaining results on behalf of SLTU Medical Staff from Referring Physicians and GPs.
- 4.2 Results should be returned to SLTU either in writing or by fax to the Transplant Co-ordinators on 0131 242 1722.
- 4.3 All abnormal results will be reviewed by SLTU consultant staff at the weekly follow-up meeting.
- 4.4 Laboratory results should be passed to the database manager for entry onto proton database prior to filing in patient's notes.

5. ROLE OF GENERAL PRACTITIONER

- 5.1 The GP's assistance in post transplant follow-up care is encouraged to facilitate on-going monitoring between hospital clinic visits and will be requested on an individual basis.
- 5.2 The GP remains the patient's first line of medical contact for all general non-transplant related health enquiries.
- 5.3 GPs can access the shared-care protocols on the Lothian Joint Formulary site at the following address <http://www.ljf.scot.nhs.uk/scp/index.html>

6. ROUTINE CLINIC DUTIES

- 6.1 Weight
- 6.2 blood pressure
- 6.3 blood sampling

6.3.1 **Routine for all visits**

6.3.1.1 Clinical Chemistry:

Na, K, CO₂, urea, creatinine, bilirubin, ALT, GGT, alkaline phosphatase albumin

-10 ml in plain (brown) monovette tube.

blood levels ciclosporin, tacrolimus or sirolimus

- 2.5 ml in EDTA (red) monovette tube.

6.3.1.2 Haematology

Full blood count

-2.5 mls in EDTA (red) monovette tube.

6.3.2 **Specific to certain categories**

6.3.2.1 Glucose - all clinic visits in first 3/12

6.3.2.2 Lipids - annually

6.3.2.3 Serum AFP - all visits 3/12 up to 1 year post-OLT in patients with a hepatoma (either as indication for transplant or as coincidental finding).

6.3.2.4 Serum anti-HBs - sample to virology

- all clinic visits in patients transplanted for hepatitis B.

6.3.2.5 Alcohol - (yellow tube to clinical chemistry)

- at all clinic visits in patients transplanted for Alcoholic Liver Disease.

6.4 History:
enquire specifically about:

- symptoms on last visit
- new symptoms
- jaundice, stool/urine colour, fever, abdo pain
- dyspepsia, vomiting, diarrhoea
- cough, dyspnoea
- headaches, paraesthesia, tremor
- fluid retention, arthralgia, fatigue

6.5 Record drugs:

6.5.1 immunosuppression

Ciclosporin (Neoral), tacrolimus (specify Prograf or Advagraf), sirolimus, azathioprine or mycophenolate, prednisolone.

6.5.2 other drugs

6.5.3 check patient's medication record book "greenbook"

6.6 Arrangements:

6.6.1 Contact for alterations in therapy

6.6.2 Next appointment

6.7 Documentation

The clinic findings will be recorded on a standard outpatient form ([Appendix I](#)).

6.8 Aide-Memoire

A laminated aide-memoire is available in clinic consultation rooms and transplant offices. ([Appendix 2](#))

7. CLINIC REVIEW

The out patients seen in the preceding week will be discussed at a weekly clinic review attended by consultant hepatologist, consultant surgeon, medical registrar and transplant co-ordinator(s). Changes in therapy and other action will then be communicated via the transplant co-ordinators on behalf of the SLTU medical staff by telephone and documented in the case notes. Alteration in therapy or other action will also be included in the clinic letter sent to the GP and referring physician.

8. IMMUNOSUPPRESSION

8.1 CALCINEURIN BLOCKER (TACROLIMUS/CICLOSPORIN)

8.1.1 Introduction

The primary immunosuppressive drug will be one of the calcineurin blockers **tacrolimus** or **ciclosporin**. The calcineurin inhibitors must be prescribed and recorded by brand name to prevent confusion.

- Tacrolimus - Prograf or Advagraf
- Ciclosporin - Neoral

8.1.2 Dosing

The dosage of tacrolimus or ciclosporin must take account of not only the blood concentration, but also the time since transplant, the history of rejection and the side effects, particularly the presence of renal impairment. Toxicity within the recommended blood concentrations can occur.

The dose of immunosuppressive drugs should take account of the relative risks of rejection - the high risk patients are those with a previous history of rejection, younger patients, females and those transplanted for auto immune diseases. (eg. autoimmune hepatitis and primary biliary cirrhosis). Severely malnourished patients and those with renal failure have a lower risk of rejection.

8.1.3 Recommended trough blood levels

8.1.3.1 Tacrolimus

0 - 3 months post transplant

5 - 15 ug/l

after 3 months post transplant 5 - 10 ug/l

8.1.3.2 Ciclosporin

0 to 6 months 100 - 150 nmol/l

6 months onwards 70 - 100 nmol/l

8.1.4 Dosage Adjustment

If patient has tacrolimus/ciclosporin concentration too high or too low, consider the reason prior to adjusting the dose, eg:

- tacrolimus/ciclosporin too high:

Did the patient take ciclosporin/tacrolimus on the day of the assay?

Has the patient taken any new drugs?

- tacrolimus/ciclosporin too low:

Is the patient compliant?

Is there impaired absorption? Vomiting or diarrhoea?

Has the patient taken any new drugs?

If adjusting dose, increase or decrease by approximately 20%

8.1.5 Tacrolimus/ciclosporin toxicity

Warning evidence of tacrolimus/ciclosporin toxicity:

headaches, paraesthesia, tremor, fits nausea, vomiting, diarrhoea

hypertension, hyperkalaemia, renal impairment, arthralgia, diabetes mellitus

8.1.6 Drug Interactions

Drug interactions with tacrolimus/ciclosporin

Assume any drug may interact with tacrolimus/ciclosporin until you know it does not.

If in doubt, contact SLTU pharmacist (Bleep 5132) and monitor U/Es, creatinine and blood tacrolimus/ciclosporin concentrations at least 2 x weekly. The following drugs are known to interact:

8.1.6.1 increase tacrolimus/ciclosporin concentration (anticipate toxicity and reduce dose or be guided by blood ciclosporin/tacrolimus concentrations measured < 1/52 after starting medication).

amiodarone
clarithromycin
danazol
diltiazem
erythromycin
fluconazole (> 200 mg/day)
itraconazole
ketoconazole
nicardipine
progestogens

8.1.6.2 reduce tacrolimus/ciclosporin concentration (anticipate increase requirements but be guided by blood concentrations measured > 1/52 tacrolimus/ciclosporin after starting medication).

carbamazepine
griseofulvin
phenobarbitone
phenytoin
primidone
rifampicin

8.1.6.3 increase risk of hyperkalaemia
potassium-sparing diuretics
ACE inhibitors - captopril etc

week 8.1.6.4 increase risk of nephrotoxicity (monitor urea + creatinine 2 x initially).

aciclovir
amphotericin
co-trimoxazole
ganciclovir
gentamicin

NSAIDs

neomycin

any nephrotoxic drugs.

8.1.7 Tacrolimus in Patients with Anaemia/Hypoalbuminaemia

if there is

Because the drug is highly red blood cell and protein bound, increased efficacy/toxicity for a given whole blood concentration will occur anaemia or hypoalbuminaemia.

8.1.8 Tacrolimus/Ciclosporin in Patients with Hepatic Dysfunction

Tacrolimus concentration is increased if hepatic function is decreased. Ciclosporin (Neoral) concentration may be reduced in severe cholestasis or steatorrhoea.

8.1.9 Shared care protocols are available at <http://www.ljf.scot.nhs.uk/scp/index.html>

8.2 PREDNISOLONE

Prednisolone is used initially as an immunosuppressant but will normally be discontinued after 3/12.

Reduce prednisolone dose as follows:

<u>TIME POST TRANSPLANT</u>	<u>DAILY DOSE</u>
0 - 3 weeks	20mg
3 - 6 weeks	15mg
6 - 9 weeks	10mg
9 - 12 weeks	5mg
after 3 months	0*

*The two exceptions to discontinuation are:

on - patients with autoimmune chronic active hepatitis who should remain

5mg/day to reduce risk of disease recurrence.

- patients with hepatitis C infection who should remain on 5mg/day for 12 months.

restart taking If the patient receives high dose steroid therapy for cellular (acute) rejection, prednisolone at 20 mg per day and reduce according to the above schedule, the episode of rejection as time zero.

8.3 AZATHIOPRINE

follows: Continue at 1 mg per kg once daily, unless bone marrow suppression as follows:

WBC	2 - 3	$\times 10^9/l$:	0.5mg per kg per day
	< 2	$\times 10^9/l$:	stop
Platelets	40 - 60	$\times 10^9/l$:	0.5mg per kg per day
	< 40	$\times 10^9/l$:	stop

8.4 MYCOPHENOLATE MOFETIL

situations: Also known simply as Mycophenolate or MMF, this drug which is a similar but more potent immunosuppressant to azathioprine, may be used in 3 situations:

8.4.1 in patients with early chronic rejection, in combination with tacrolimus.

8.4.2 in patients with renal impairment to allow either

8.4.2.1 Replacement of CNI with MMF and Prednisolone

8.4.2.1 Dose reduction of CNI in combination with MMF.

The dosage is 1 - 2g/day. It is less prone to causing marrow suppression than azathioprine but has significant risk of GI intolerance, both nausea and diarrhoea, which can be reduced by introducing the drug in a step wise manner and dividing the daily dose.

8.4.3 The sequence of steps in patients with mild-moderate renal impairment more than 6 months after transplant and with normal graft function is as follows:

- i) 24 hr urine for urinary protein and creatinine clearance.
- ii) Renal ultrasound

If creatinine clearance in range 20 - 70ml/min and investigations do not suggest renal impairment for reasons other than CNI toxicity and therefore changing from CNI to MMF and prednisolone.

- iii) Commence MMF 500mg bd, increasing to 1g bd if no side effects.
- iv) Once established on full dose MMF, commence prednisolone 10mg/day and half dose of CNI.

- v) Continue to half dose of CNI at monthly intervals until discontinued all together, providing LFTs remain normal.
- vi) Reduce Prednisolone to 7.5mg. Further reduction should be discussed with consultant hepatologist.

8.5 SIROLIMUS

Also known as Rapamune, used as renal-sparing immunosuppressant in a similar way to mycophenolate or in patients with HCV recurrence who cannot tolerate treatment.

Side effects of Sirolimus include delayed wound healing, dyslipidaemia, marrow suppression, haemolysis and proteinuria.

If changing from CNI to Sirolimus

- (i) Commence Sirolimus at 2mg once a day.
-If there are concerns about the patients white count consider starting on 1mg Sirolimus and leaving half-dose CNI until trough level available.
- (ii) Half-dose of Tacrolimus for three days then stop. (If on Ciclosporin dose should also be halved but needs to be taken at least 4 hours before or after Sirolimus)
- (iii) Azathioprine or MMF should not be discontinued until 1 month post change over.
- (iv) Urine specimen should be tested for protein, if protein patient should be asked to bring 24 hours urine specimen to next clinic.
- (v) FBC, LFTs and Sirolimus level should be checked after 7-10 days
- (vi) Trough levels should be taken as with CNIs
- (vii) Levels 4-6ng/ml (be guided by the LFTs)

As Sirolimus is not licensed in liver transplantation GPs may not be willing to prescribe - in this case contact Janice Davidson, Senior Research Nurse, to organise supplies.

8.6 OTHER DRUGS

At 3 months post-transplant, the following drugs can be discontinued:

ranitidine
 fluconazole
 co-trimoxazole
 valganciclovir

<u>IMMUNOSUPPRESSION</u>		Before altering dose
Tacrolimus 15	Target: First 3 months: 5 – Thereafter: 5 –	1) think <u>why</u> is the result off? eg. <ul style="list-style-type: none"> • interaction with new drug? • inadvertently took morning dose? • lab error.
Cyclosporin – 200	Target: First 3 months: 150 – Thereafter: 100 –	2) Consider graft function & toxicity (renal, BP) as well as blood level.
If adjusting, change dose by ~ 20%		
Azathioprine only change if strong suspicion of toxicity. Remember mild neutropaenia due to persistent hypersplenism in common post-OLT.		

Steroids should only be on prednisolone if:

- 1) within 3 months of OLT
- 2) within 3 months of episode of rejection
- 3) autoimmune hepatitis
- 4) HCV if within 12 months of OLT
- 5) other indication (eg. IBD)

COMPLICATIONS: Calculate CVD risk from attached chart or BNF.

Hypertension	Renal function
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<p>Treat if 1. BP > 160/100</p> <p>BP > 149/90 and i) established CVD</p> <p style="padding-left: 40px;">ii) 10 yr risk CVD > 20%</p> <p style="padding-left: 40px;">iii) diabetic</p>	<p>Cholesterol</p> <p>Treat if 1. ↑ level</p> <p>Hypertension & established CVD</p> <p>Hypertension, age > 40, CVD risk > 20%</p> <p>Drug of choice: Fluvistatin 20 – 80 mg/day</p> <p>Do <u>not</u> treat if significant graft dysfunction</p> <p style="text-align: right;">LFTs worsen on therapy</p>
<p>Before commencing therapy, ensure pred. stopped/minimised & CNI levels non-toxic</p>	

<p>1st line: Amlodipine 5 – 10 mg/day</p> <p>2nd line: ACE/ Angiotensin II receptor blocker</p> <p>3rd line Bendrofluazide / Atenolol/ Doxazosin</p>	<p>Diabetes</p>
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Appendix 10: Part of the In-patient protocol

Results of viral culture of tissue, and blood will first be available two days later. CMV PCR results are currently available on Wednesday and Friday. If CMV infection is proven, patients will receive IV ganciclovir 5 mg/kg bd for 14 days. (Reduce dose in renal impairment - discuss with Pharmacist, Bleep 5132). Alternatively, if well, they can be converted to oral Valganciclovir 900 mg twice daily.

7. **IMMUNOSUPPRESSION**

Standard starting immunosuppression regime is given in [appendix 9](#).

Tacrolimus will be commenced on the first post operative day. The starting dose of Tacrolimus is 0.05 mg/kg bd. The starting dose of Ciclosporin is 4 mg/kg bd. These dosages should be halved in patients with renal impairment.

7.1 **CALCINEURIN BLOCKER (TACROLIMUS/CICLOSPORIN)**

7.1.1 Introduction

The primary immunosuppressive drug will be one of the calcineurin blockers **Tacrolimus** or **Ciclosporin**. Tacrolimus is available as Prograf (twice daily) and Advagraf (once daily). Prograf is to be prescribed following liver transplantation. Ciclosporin is to be prescribed as Neoral.

7.1.2 Dosing

The dosage of Tacrolimus or Ciclosporin must take account of not only the blood concentration, but also the time since transplant, the history of rejection and the side effects, particularly the presence of renal impairment. Toxicity within the recommended blood concentrations can occur.

The dose of immunosuppressive drugs should take account of the relative risks of rejection - the high risk patients are those with a previous history of rejection, younger patients, females and those transplanted for auto immune diseases eg. autoimmune hepatitis and primary biliary cirrhosis. Severely malnourished patients and those with renal failure have a lower risk of rejection.

7.1.3 Recommended trough blood levels

7.1.3.1 **Tacrolimus**

0 - 3 months post transplant	5 - 15 ug/l
after 3 months post transplant	5 - 10 ug/l

7.1.6.3 **Ciclosporin**

0 to 6 months	100 - 150 nmol/l
6 months onwards	70 - 100 nmol/l

7.1.4 Dosage Adjustment

If patient has Tacrolimus/Ciclosporin concentration too high or too low, consider the reason prior to adjusting the dose, eg:

- Tacrolimus/Ciclosporin too high:
 - Did the patient take Ciclosporin/Tacrolimus on the day of the assay?
 - Has the patient taken any new drugs?
- Tacrolimus/ Ciclosporin too low:
 - Is the patient compliant?
 - Is there impaired absorption? Vomiting or diarrhoea?
- Has the patient taken any new drugs?

If adjusting dose, increase or decrease by approximately 20%

7.1.5 Tacrolimus/Ciclosporin toxicity

Warning evidence of Tacrolimus/Ciclosporin toxicity:

Headaches, paraesthesia, tremor, fits, nausea, vomiting, diarrhoea
hypertension, hyperkalaemia, renal impairment, arthralgia, diabetes mellitus

7.1.6 Drug Interactions

Drug interactions with Tacrolimus/Ciclosporin

Assume any drug may interact with Tacrolimus/Ciclosporin until you know it does not. If in doubt, contact SLTU pharmacist (Bleep 5132) and monitor

U/Es, creatinine and blood Tacrolimus/Ciclosporin concentrations at least 2 x weekly.

7.1.6.1 The following drugs are known to increase Tacrolimus/Ciclosporin concentration (anticipate toxicity and reduce dose or be guided by blood Ciclosporin/Tacrolimus concentrations measured < 1/52 after starting medication).

- amiodarone
- anti-retroviral therapy
- clarithromycin
- danazol
- diltiazem
- erythromycin
- fluconazole (> 200 mg/day)
- itraconazole
- ketoconazole
- nifedipine
- progestogens

7.1.6.2 The following drugs reduce Tacrolimus/Ciclosporin concentration (anticipate increase requirements but be guided by blood Tacrolimus/Ciclosporin concentrations measured < 1/52 after starting medication).

- carbamazepine
- caspofungin
- griseofulvin
- phenobarbitone
- phenytoin
- primidone
- rifampicin

7.1.6.3 Anti-retroviral therapy: several of the drugs used for HIV infection interact with CNIs. Often patients require only once weekly dosing with Tacrolimus, (however be aware certain drugs may also *reduce* the Tacrolimus concentrations).
Patients transplanted who are HIV positive and on anti-retroviral therapy will be managed jointly with Professor Clifford Leen from the Regional Infectious Diseases Unit at WGH.

7.1.6.4 The following drugs increase the risk of hyperkalaemia

- potassium-sparing diuretics
- ACE inhibitors - lisinopril etc

7.1.6.5 The following drugs increase risk of nephrotoxicity (monitor urea + creatinine 2 x week initially).

- acyclovir
- amphotericin
- co-trimoxazole
- ganciclovir
- gentamycin
- NSAIDs
- neomycin
- valgancyclovir
- vancomycin
- any nephrotoxic drugs.

7.1.7 Tacrolimus in patients with anaemia/hypoalbuminaemia

Because the drug is highly red blood cell and protein bound, increased efficacy/toxicity for a given whole blood concentration will occur if there is anaemia or hypoalbuminaemia.

7.1.8 Tacrolimus/Ciclosporin in patients with hepatic dysfunction

Tacrolimus concentration is increased if hepatic function is decreased. Neoral, the newer form of Ciclosporin is more water soluble than Sandimmun, its fat soluble predecessor (which has now been withdrawn) but its concentration may be reduced in severe cholestasis or steatorrhoea.

7.2 BASILIXIMAB

This interleukin-2 receptor antagonist will be given in elective patients with serum creatinine > 150 micromol/l or eGFR < 40 ml/min. The first dose (20mg) will be given within the first 24 hours after transplantation. The second dose (20mg) will be given on Day 4.

Mycophenolate Mofetil (MMF) will be given instead of azathioprine commencing at 500mg bd and increasing to 1g bd.

Tacrolimus will be commenced on day 7 aiming for trough levels 4-7.

7.3 CORTICOSTEROIDS

7.3.1 Intravenous Hydrocortisone 100mg bd by bolus injection starting immediately post-operative and stopping when oral intake established.

7.3.2 Oral Prednisolone 20mg per day starting once oral intake established. The non-enteric coated 5mg tablets will be used. The dose will be reduced monthly by 5mg increments every 3 weeks and discontinued at three months post-op (with

the exception of patients transplanted for autoimmune hepatitis who should continue 5mg /day indefinitely to decrease risk of disease recurrence and patients transplanted for hepatitis C who should remain on 5mg/day for around 12 months). This regime is flexible and may require alteration according to degree of rejection and corticosteroid side effects.

While the patient is receiving corticosteroids, ranitidine 150mg bd orally or 50mg tds IV will be given as prophylaxis against stress ulceration.

7.4 AZATHIOPRINE

7.4.1 Intravenous: 1 mg/kg/day once daily starting immediately post-operative and continued until oral intake established.

7.4.2 Oral: same dose (1 mg/kg/day) once daily from when oral intake established.

7.4.3 Marrow suppression: Azathioprine doses may be reduced according to the peripheral WBC and platelet counts, which often remain low post operatively.

The dose should be adjusted to the formula -

WBC	2 - 3 x10 ⁹ /L:	0.5 mg/kg
WBC	< 2 x10 ⁹ /L:	stop
Platelets	40 - 60 x10 ⁹ /L:	0.5 mg/kg
Platelets	< 40 x10 ⁹ /L:	stop

7.5 GRAFT REJECTION (see [appendix 10](#))

Decisions on treatment of rejection will be made in consultation with the consultant hepatologist. If acute (cellular) rejection is suspected, e.g. fever, jaundice, elevated transaminases; a liver biopsy will be performed.

If acute rejection is confirmed, treat as follows -

- Mild: Observe
 - Moderate/Severe methylprednisolone 1 g/day for 3 days
- If clinical and biochemical improvement, simply observe.
 - If no improvement, re-biopsy.
 - If continuing rejection, repeat above methylprednisolone treatment.
 - If rejection recurs/persists after 2 cycles of methylprednisolone -
 - a) Ensure diagnosis is correct
 - b) if on ciclosporin, convert to tacrolimus.