Cambridgeshire NHS
Health Authority

METHOTREXATE TOXICITY

AN INQUIRY INTO THE DEATH OF A CAMBRIDGESHIRE PATIENT IN APRIL 2000

CAMBRIDGESHIRE HEALTH AUTHORITY

JULY 2000

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1 INTRODUCTION

1.1 This report sets out the facts in the case of a Cambridgeshire resident who died as a result of a serious untoward incident within the local health authority area. The Health Authority has conducted an Inquiry into the incident which resulted from failures in the care and treatment of the patient throughout the patient's whole care pathway.

2 BACKGROUND

2.1 The daughter of the patient telephoned the complaints department at the Cambridgeshire Health Authority on 26 April 2000 to report her concern about the circumstances leading up to her mother's illness. At this time the patient was in hospital having been admitted on 18 April with a very sore throat and a severe skin rash.

2.2 The daughter had been advised by the hospital that it was likely that her mother's symptoms were due to having taken a daily dose of the drug Methotrexate. The patient had been taking a weekly dose of Methotrexate for rheumatoid arthritis. The strength of Methotrexate had inadvertently, recently been altered by her General Practitioner (GP) to 10 mg as a daily dose from the patient's usual single weekly dose of 17.5 mg (see Appendix 1). The result was that the patient had been inadvertently overdosing and her immune system had become severely compromised. The hospital had continued to treat the patient with this high daily dosage until the mistake was identified on the fourth day of her admission.

2.3 The daughter wished to bring this matter to the attention of the Health Authority. She was not sure whether the high daily dosage of Methotrexate was due to a prescribing or dispensing error and felt that an investigation should be carried out.

2.4 On 30 April 2000 the patient died.

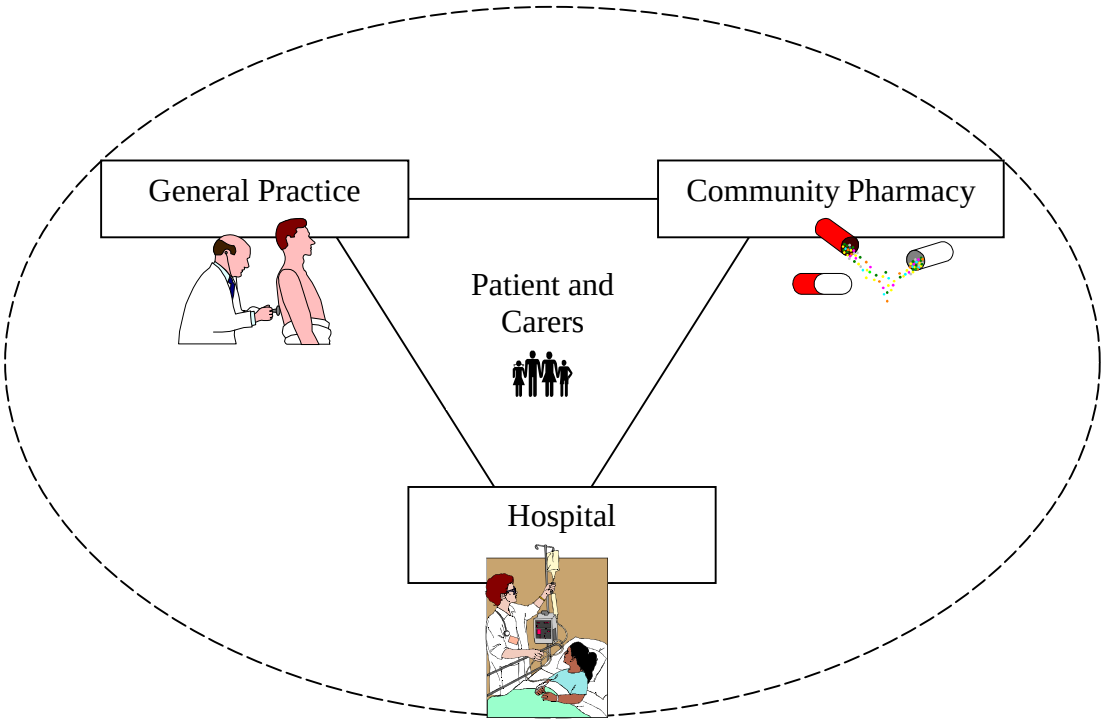
3 CONTEXT

3.1 The NHS Executive Serious Untoward Incident Procedure defines a serious untoward incident, which applied to this circumstance, as 'an incident on an NHS site or elsewhere whilst in NHS-funded or NHS regulated care involving: a) NHS patients … and which: caused death' (see Appendix 2). The procedure sets out guidance that all serious untoward incidents should be investigated to establish what, if any, lessons arising need to be incorporated into future practice.

3.2 At the time it appeared that this tragic incident could have resulted because of possible failures in care and treatment throughout the patient's whole care pathway, involving shared care arrangements within the NHS in Cambridgeshire between the patient and her carers, general practice, community pharmacy and a hospital.

3.3 The diagram below shows the NHS organisations which had an active responsibility in successfully delivering the patient's shared care arrangements.

Diagram of Shared Care Arrangement



3.4 As this incident appeared to have resulted from failings within all stages of the patient's care pathway, the Health Authority gained approval from the NHS Executive Eastern Regional Office, and agreement of all the organisations involved in the incident, to conduct an Inquiry into events within each of these care settings under the guidance set out in the NHS Executive Serious Untoward Incident Procedure. The guidance recommends that the internal Inquiry should be completed quickly and if possible within 28 days.

4 PURPOSE OF INQURY

4.1 With the agreement of all parties concerned, the Terms of Reference were established for the Inquiry:

- To inquire into the prescribing, dispensing, administration and events in community and hospital settings which led to the patient taking a toxic dosage of Methotrexate.
- To make recommendations to the Health Authority and others on how to minimise the risk of future similar occurrences.

5 MEMBERSHIP OF INQUIRY PANEL

5.1 In order to ensure that the necessary expertise and independence were available to the Inquiry, the Panel was constituted with the agreement of all the parties involved (see Appendix 3). The constitution of the Panel ensured leadership by a lay member of the

Health Authority, and professional inputs from general practice, community pharmacy and a hospital specialist.

6 MEETINGS OF THE INQUIRY PANEL

6.1 The Inquiry Panel met on four occasions for a total of 16 hours (see Appendix 4). A considerable amount of time was also spent outside these meetings collecting and collating written evidence, following up enquiries and visiting the GP practice and the community pharmacy involved in this incident.

7 SOURCES OF EVIDENCE FOR THE INQUIRY PANEL

7.1 A substantial amount of information (see Appendix 5) was provided in order to assist the Panel in reaching its conclusions. This information provided the Panel members with a large amount of detail specific to the care and treatment of the patient and also provided background information on the patient's condition, the drug Methotrexate and reports produced by the parties involved in response to specific questions raised by the family.

7.2 The report seeks to lay out the facts about the case and to advise what lessons should be learnt from them. The Inquiry is not a disciplinary process and any criminal, legal, contractual or professional performance procedures will need to be considered outside this Inquiry.

7.3 The Panel chose to structure its investigation and the ensuing report by outlining the chronology of events, identifying critical points in the chronology and linking its findings and recommendations to these. A summary of the chronology of critical events is given in section 10 to provide an overview. Clearly the nature of the drug and its use in the treatment of rheumatoid arthritis are crucial as are the steps from prescription to administration of the drug.

7.4 The Panel would like to thank all the parties involved for their co-operation in the Inquiry.

8 METHOTREXATE

8.1 Methotrexate is a folic acid antagonist and is classified as an antimetabolite cytotoxic immunosuppressant agent. It has been used for many years as a therapy for cancers such as leukaemias, lymphomas and solid tumours such as breast and lung cancer. It is also used to treat severe forms of psoriasis, a chronic skin disease, and for the last 10 – 15 years it has been widely used as a disease modifying drug for rheumatoid arthritis.

8.2 Because of its potential toxicity, Methotrexate needs to be carefully monitored particularly for adverse effects on the bone marrow and liver. The side effect profile is extensive and there are a number of interactions with commonly used drugs. In the

treatment of psoriasis the drug is given weekly. Regular (1-3 monthly) blood tests, especially full blood counts and liver function tests, are mandatory.

8.3 The suppliers of Methotrexate tablets market 2.5 mg and 10 mg strengths as yellow tablets. The 2.5 mg tablet is scored on one side with M2.5 and is pale yellow whilst the 10 mg tablet is scored M10 and is a deeper yellow colour. The tablets are the same size and shape. Neither Pharmacia and Upjohn nor Faulding lists rheumatoid arthritis as an indication for its use. The drugs are supplied in bottles of 100 tablets with a single information sheet.

8.4 A third company, Wyeth, does list rheumatoid arthritis as a licensed indication for the use of methotrexate. It markets only a 2.5 mg tablet which is supplied in a blister pack containing 28 tablets. Patient information sheets and advice to GP prescribers about methotrexate are provided by national organisations such as the Arthritis Research Campaign and the British Society for Rheumatology (Appendix 6). Examples of written information and advice from local rheumatologists to GP prescribers and patients involved in shared care arrangements are shown in Appendix 7.

9 PRESCRIBING, DISPENSING AND ADMINISTERING DRUG TREATMENTS

9.1 There are at least three clear steps that are taken from the point at which a doctor decides to prescribe a drug for the treatment of a condition, the prescription is dispensed by a pharmacist and then the prescribed drug is administered to the patient. These steps are shown diagrammatically below.

STEP		RESPONSIBILITY
1 Prescribing	– doctor	Doctor has responsibility for writing the prescription
↓		
2 Dispensing	– pharmacist	Pharmacist has responsibility for assessing safety, quality and efficacy of the drug treatment prescribed and for dispensing the correct medication
↓		
3 Administering to patient	– patient/carer/ nurse	Patient/carer/nurse has responsibility for administering the medication as directed

9.2 As the diagram illustrates, there are different responsibilities at each stage of the process.

10 FINDINGS OF THE PANEL

Summary Chronology Of Critical Events

January 1997	• Patient commences Methotrexate treatment for rheumatoid arthritis • Shared care arrangements are put in place and the dose of Methotrexate is increased incrementally over the next six months to 17.5 mg once a week
January 2000	• Patient undergoes right total knee replacement • Within hospital Methotrexate dosage and regime altered from 17.5 mg weekly to one 2.5 mg dose during her entire stay of 8 days
6 April 2000	• Patient and daughter ask GP A to prescribe Methotrexate in a way that involves taking fewer tablets, as experienced in hospital during the patient's January 2000 admission. GP A inadvertently writes prescription for Methotrexate 10 mg tablets once daily without withdrawing the previously prescribed 2.5 mg tablets (see Appendix 1) • Community Pharmacist dispenses Methotrexate 10 mg once daily
7 April 2000	• Patient starts taking 10 mg tablet once daily. This is a total weekly dose of 70 mg
12 April 2000	• GP B identifies prescription error on repeat prescription request and crosses it off. Error remains unrectified on computer held record
13 April 2000	• Patient begins to feel unwell
14 April 2000	• Telephone consultation between patient's daughter and GP C regarding patient's condition. Treatments prescribed for sore mouth and vagina
15 April 2000	• GP C carries out a home visit to patient and offers admission to hospital
17 April 2000	• Patient's condition continuing to deteriorate • GP A visits patient at home
18 April 2000	• Following telephone conversation with daughter GP A arranges hospital admission to ENT ward with Dr D • GP A faxes patient information to Dr D relating to admission. Fax sent but not received by Dr D • Dr D admits patient and reviews patient's own drugs brought into hospital • Blood tests ordered (but two successive samples inadequate for blood counts and not followed through)
19 April 2000	• Drug chart indicates 100 mg daily of Methotrexate • Staff Nurse identifies incorrect dosage and administers 10 mg only • Drug chart not changed
20 April 2000	• Hospital pharmacy queries Methotrexate dose on receipt of patient's drug chart (asks nurse to tell Dr to check dose) • Dr D phones GP surgery and gets confirmation from a non medical member of staff that 10 mg daily is the correct prescription • Methotrexate 10 mg administered

21 April 2000	• Patient's condition deteriorating • Methotrexate 10 mg administered
22 April 2000	• Nurse suggests to Dr E that Methotrexate could be cause of problem • Dr E notes blood count results still outstanding and chases these • Blood tests reveal problem which was caused by Methotrexate overdose • Patient transferred to care of Haematology team
30 April 2000	• Patient dies

10.1 The findings of the Panel are presented below.

1982 - Critical Event 1

- The patient developed rheumatoid arthritis.

1984 - Critical Event 2

- Patient was prescribed Penicillamine by a hospital consultant. Shared care arrangements were put in place between the hospital and primary care. This included the patient holding a results booklet to assist with the monitoring of her treatment.

Panel Observations

- Shared care arrangements appear to have been sound. Family recall booklet used to monitor Penicillamine.

January 1997 - Critical Event 3

- After stopping Penicillamine the patient was prescribed Methotrexate by a hospital consultant for treatment of her rheumatoid arthritis. Shared care arrangements were put in place. As part of this arrangement the GP Practice took responsibility for monitoring Methotrexate (performing regular blood tests and reporting to hospital). The hospital consultant was responsible for any change in dose. Subsequent repeat prescriptions were provided by the GP
- The regular dosage was 17.5 mg Methotrexate per week (7 x 2.5 mg tablets) taken once weekly.

Panel Observations

- GPs clear about their responsibilities within the shared care protocol. Patient's competence appears to have been sound. Over the period 1997 to January 2000 there appears to have been effective control of the condition via Methotrexate therapy through shared care arrangements.
- There is no written confirmation that patient information about Methotrexate was given either verbally or in writing from any source. Patient's hospital records record the hospital doctor's decision to start Methotrexate therefore it can be assumed this would have been an informed decision to change from Penicillamine to Methotrexate following discussion between the patient and hospital doctor. The family have no recollection of the patient having been given any written information about Methotrexate nor having a shared care results booklet to assist with monitoring.

January 2000 - Critical Event 4

- The patient is admitted to hospital for a right total knee replacement. During this admission the patient's Methotrexate dose and regime was altered with the effect that whilst in hospital the patient took just one Methotrexate tablet during her 8 day admission. Hospital notes indicate this was one 2.5 mg tablet of Methotrexate.

Panel Observations

- The Panel feel this was a significant event because while admitted the patient had received only one tablet of Methotrexate which had caused fewer side effects for her and proved much simpler to take. Hospital records show that in fact this had not been the full dose of 17.5 mg weekly, but the patient had not understood this. This event seeded the idea that her regime of seven 2.5 mg tablets once a week could be modified to a simpler regime. Following discharge from hospital the patient resumed her former regime of 17.5 mg weekly (7 x 2.5 mg tablets once a week).

Thursday 6 April 2000 - Critical Event 5

- The patient together with her daughter has a consultation with GP A for phlebitis in her left leg and pain in her right knee. GP A is a locum GP. At the end of the consultation the daughter comments on the change in regime for methotrexate whilst patient was in hospital in January 2000 and explains that this suited her mother well. The daughter asked the GP if methotrexate could be prescribed in such a way that her mother could take fewer methotrexate tablets. GP A agrees and issues a prescription for Methotrexate 10mg daily although the intention had been 10 mg 'as directed'. No record is made in the written patient notes of the change in prescription but 10 mg daily is recorded on the current computer record.
- Signed prescription shows 10 mg once daily.
- Later that day, the patient's husband visits the local community pharmacy to obtain the revised Methotrexate prescription. A Locum Community Pharmacist is on duty, practising alone, and dispenses 30 tablets of Methotrexate 10mg to be taken daily.
- As this was a new prescription, this action would have required the pharmacist to type into their computer a new dose for the first time.

Panel Observations

- It appears that GP A had no intention to change the patient's total weekly dose of 17.5 mg, but to simplify it by reducing the number of tablets to be taken from 7 tablets to 4 once weekly (1 x 10mg and 3 x 2.5mg – the patient already had a supply of 2.5mg tablets) (see Appendix 1). However, it has been identified that GP A made an inputting error into the practice-based computer entering the abbreviation `od` (once daily) instead of `asd` (as directed) into the computer. This error resulted in the prescription being generated from the computer stating Methotrexate 10 mg daily. At the time of this event the General Practice's computer system did not have any warning message about Methotrexate and its weekly dosage regime. We are aware that this prescribing decision was made at the end of the consultation and it is unclear what discussion took place between the patient and GP about this new regime.
- The Panel accepts that with this shared care protocol a GP would not normally change the actual dose of Methotrexate without a discussion with the hospital consultant. It however would be quite acceptable for a GP to change the number

of tablets making up the dose without prior discussion with hospital. Such a change should however be communicated to those involved in shared care arrangements.

- We note the fact that the patient was on an immunosuppressant such as Methotrexate which was not flagged up prominently in either the GP written records or computer prescribing system.
- Locum Community Pharmacist working single handed checked the Methotrexate dose given on the prescription but did not query the frequency. We note that as this was not a repeat prescription the pharmacist would have had to actively change the computer record. The pharmacist does not recollect dispensing the prescription at all. This was the pharmacy normally used by the patient which would have records of previous prescriptions.
- We note that in pharmacies where there is a dispensing assistant, the pharmacist would have worked through a checking procedure jointly which is then documented. If a pharmacist has any doubt about the prescription they would normally contact the prescribing doctor to discuss their concerns. Clearly the pharmacist did not recognise the prescribing error, and therefore did not contact the GP.
- The Panel have observed that the 2.5 mg and 10 mg Methotrexate tablets are both yellow in colour and look very similar. Also there have been other recorded cases of Methotrexate prescribing errors across the country and concern expressed by professionals about the difficulty and risks associated with Methotrexate prescribing. At the time of this event, the pharmacy computer system did not have any warning message about Methotrexate and its weekly dosage regime.
- There are concerns about the pharmacy using supplies of methotrexate from different sources/manufacturers, some of which are not licensed for use in rheumatoid arthritis and which therefore do not provide suitable product information.

Friday 7 April 2000 - Critical Event 6

- The patient starts to take one 10mg tablet daily following the directions printed on the medicine bottle.

Panel Observations

- The patient is part of the shared care team and therefore should be seen as a partner in her care with an active role in her own care. She had been taking a weekly regime of the drug since 1997 and attended the GP Practice monthly for blood tests. Prior to her final illness she was felt to be competent to self administer her medication and was well supported by her immediate family.

Wednesday 12 April 2000 - Critical Event 7

- In the practice, GP B is on duty signing repeat prescriptions and received a repeat prescription request from the patient. GP B recognised that the dose of Methotrexate was incorrect, and interpreted this as a one off error by the staff producing the prescription. It seemed impossible to GP B that such a dose could have been previously prescribed or dispensed. He therefore crossed out the Methotrexate on the prescription anticipating that a correct prescription would consequently be presented for signing. GP B did not inspect or change the patient's computer drug record. A note was attached to the prescription

asking practice staff to check the request. The practice is unable to explain why this was not acted upon.

Panel Observations

- Error identified but not followed through rigorously therefore the incorrect dosage continued to be taken by patient and the error remained on GP computer system. A thorough process would have involved reviewing the written medical records, identifying the original prescriber, and, having confirmed the error, deleting the prescription details fully from the computer system and contacting the patient to ensure the appropriate dose was being taken.
- We note that the repeat prescription request for Methotrexate was made very shortly, just six days after the prescription was first dispensed, even if 10 mg daily was correct. In addition, the Methotrexate repeat request slip had been altered by hand. Again this should have led to further enquiries.

Thursday 13 April 2000 - Critical Event 8

- The patient begins to feel unwell.

Friday 14 April 2000 - Critical Event 9

- The daughter telephones GP practice and speaks with GP C regarding the patient's sore mouth and vagina. GP C gives telephone advice and issues treatments on the basis of the telephone conversation.
- GP C refers to patient's written medical records during this conversation and records action in those notes; however electronic computer based prescription records were not referred to.

Panel Observations

- Two sets of patient notes are commonly used by a GP: hard (hand-written) copy and computer record. The new Methotrexate prescription was not recorded in the hand-written notes by GP A therefore no reference for GP C to see. Additionally the medical records did not flag up prominently the patient was taking Methotrexate, and so the GP dealing with telephone call was not alerted to this.

Saturday 15 April 2000 - Critical Event 10

- The General Practice receives a request for home visit to the patient. GP C, the doctor on duty, visits and offers to arrange patient's admission to hospital. This is declined by the patient and her family. It is agreed the practice would telephone the patient on Monday if the family have not called sooner.
- The home visit is conducted with no patient notes to refer to which would be usual practice for a Saturday. GP C makes contemporaneous notes which were stuck into the patient's medical notes on the following Monday.

Panel Observations

- We note that the visit was conducted at a weekend without the benefit of the medical records. This is increasingly common with out of hours arrangements and makes the benefit of patient held information in patients with chronic disease and complex medication more important.

Monday 17 April 2000 - Critical Event 11

- GP A visits patient at home (following a request) and takes patient notes. Patient has sore throat and inflammation in her groin area.

Panel Observations

- The simultaneous timing of the perineal rash and sore throat dates back to the original telephone consultation on 14 April. The presenting complaint was not just a sore throat.

Tuesday 18 April 2000 - Critical Event 12

- Message for GP A from daughter that patient's condition has worsened. GP A contacts the daughter and discusses patient's condition over the telephone. GP A arranges admission to a hospital ENT ward because patient's main symptoms related to her sore throat. GP A has a telephone conversation with Dr D, an ENT junior doctor, at the hospital.
- GP A faxes Dr D information relevant to the patient's admission. This fax was not received by Dr D and not followed up. The fax contained no specific reference to Methotrexate, but did indicate that the patient would "bring all medication with her".
- 4.00pm: patient admitted to hospital by Dr D who recorded patient history and drugs brought in by patient (Patient Own Drugs – PODs). Methotrexate 10 mg was noted in the drug history but the frequency was not recorded. Dr D also completed a drugs chart which included a prescription for 100 mg of Methotrexate daily. As Methotrexate is not held as a stock drug on the ENT ward, the ward decided to use the patient's own drug which is within hospital procedure.
- In addition, blood tests were ordered. The full blood count was not analysed by the laboratory, as the sample was not satisfactory.
- During the night Dr E reviews patient, notes the blood test had been unsuccessful as it had clotted. Dr E takes a second blood sample and sends off to laboratory.

Panel Observations

- Panel considered whether ENT wards are appropriate for the emergency admission of elderly patients with chronic disease and undifferentiated problems.
- System for receiving faxed referral letter was unsatisfactory. The fax machine ran out of paper so only one page was received when the fax was found in a filing tray in the doctors' office (where the fax machine is located) after the patient had died.
- From reviewing the clerking notes there appears to have been a limited physical examination and patient history sought on admission. Immunosuppressant therapy was not highlighted. The 100 mg entry on the drug chart was an error which was subsequently picked up by the nursing staff.
- The Panel note there is no ward pharmacy service to the ENT ward.
- The practice of using Patient's Own Drugs (PODs) is increasingly common and carries an element of risk with potential confusion between prescriber, dispenser and administering responsibilities. However the Panel recognise there are benefits to the POD system for a large number of patients, such as immediate access to a patient's own drugs.
- The Panel note that the one blood test which remained outstanding was the single most important investigation which would have contributed to the diagnosis.

Wednesday 19 April 2000 - Critical Event 13

- 3.37 am the test on the second blood sample was reported on by the laboratory, when it was recorded as "insufficient for testing, please repeat".
- During the morning drug round, Staff Nurse F notes 100mg Methotrexate daily recorded on the patient's drug chart. Staff Nurse F realised this dose must be incorrect and confirmed with the patient that this should be 10 mg daily. Staff Nurse F then administered 10mg. Staff Nurse F leaves a post-it note for ENT SHO to amend the drug chart. No change is made by SHO on this day.

Panel Observations

- A dosage error of this order involving this type of drug should have been amended as a matter of urgency. Systems of communication between nurses and doctors need to be formalised with a robust system of checking communication has been actioned appropriately. Use of `post it` notes for the amendment of therapy are inherently unsafe.
- The Panel note that the one blood test which was unsatisfactory and the repeat sample undertaken in a timely fashion which was clotted, was the single most important investigation which would have contributed to successful diagnosis.
- Once again, the Panel note that the one blood test which still remained outstanding was the single most important investigation which would have contributed to the diagnosis.

Thursday 20 April 2000 - Critical Event 14

- Staff Nurse G responsible for drugs round and notices prescription for Methotrexate 100 mg whereas drug bottle marked 10 mg. Staff Nurse G checks with patient, notes Staff Nurse F administered 10 mg. Written 'post-it' note for ENT SHO to amend drug chart still attached. Drug chart sent down to Pharmacy later that morning for other drugs patient needed.
- At lunchtime the hospital pharmacy queries Methotrexate on receipt of patient's drug chart. Hospital Pharmacist H realises Methotrexate 100mg is wrong and crosses Methotrexate off drug chart. Pharmacist H tells Staff Nurse F that the doctor needs to clarify the correct and intended dose.
- Staff Nurse F passes message to Dr D who telephoned the GP Surgery to check dose and someone (not a GP) at the surgery confirms the dose as 10mg per day after checking the computer records.
- Dr D amends the dose on the prescription chart to re-prescribe 10 mg Methotrexate once per day.
- Dr D asks Staff Nurse F why she had not been asked to amend the prescription earlier. Staff Nurse F explained that she had written a note but that this had not been seen and was no longer attached to the drug chart.

Panel Observations

- The Panel observe that the daily ward round failed to amend the error on the drug chart. The ward round also failed to follow up the need to repeat the blood test.
- When the drug chart was scrutinised by the hospital pharmacist he correctly identified the prescribing error 100 mg and immediately crossed this off the drug chart. In addition he identified the need to check the prescription with the original prescriber. It would have been appropriate for the hospital pharmacist to contact the hospital doctor directly rather than through the nursing staff.

- The hospital doctor who contacted the practice did not speak directly to the GP prescriber. The Panel recognise that hospital doctors sometimes have difficulty contacting GPs direct as they are holding patient consultations or conducting patient visits.
- Individuals have a responsibility to ensure communications are delivered in order to be effective.
- Doctors in training who may not have experience of more rarely used drugs should be encouraged to use standard prescribing support resources such as the British National Formulary (BNF) or fellow professionals such as pharmacists.

Friday 21 April 2000 (Good Friday) - Critical Event 15

- During the ward round, doctors thought the patient's condition much improved. By this stage patient has been reviewed by two Specialist Registrars (SpRs) and two Senior House Officers (SHOs) during her stay but no evidence yet of consultant review. Ibuprofen stopped but other drugs not obviously considered. Methotrexate 10mg dose administered.

Panel Observations

- By this stage the patient had been seen regularly by the ward doctors which included four doctors in various stages of training. The patient's condition although appearing "much improved" with hindsight continued to deteriorate and there did not appear to be a satisfactory diagnosis of the cause of her condition. Consultant and/or experienced medical inputs should have been sought.
- We note that one of the side effects of Methotrexate is gastric symptoms and non steroidal drugs such as Ibuprofen interact with Methotrexate worsening the effect. The patient had been on Ibruprofen for a considerable time.

Saturday 22 April 2000 - Critical Event 16

- Staff Nurse G notes patient had developed a rash over her trunk. The senior nurse on duty asks Staff Nurse G to review the patient's medication in the BNF. Staff Nurse G contacts Dr E and suggests that Methotrexate might be the cause of the patient's problems. Dr E said he thought this was unlikely, however said he would review the patient when he was available and arrives to see the patient 40 minutes later. Dr E examines the patient and reviews the drug history. Notes blood count results are still outstanding and need to be chased. A third blood sample taken which reveals abnormalities (low blood platelets and low white blood cells). Arrangements are made to transfer the patient to the specialist haematologist team.

Panel Observations

- The nurses to their credit through attention to the patient's condition sought further information on probable cause.
- Inadequate blood samples had not been followed up during the daily ward rounds.

Sunday 23 April 2000 - Critical Event 17

- Haematology/oncology doctor explains poor prognosis to relative(s)

Panel Observations

- Despite intensive treatments in a specialised haematology ward the patient's condition continues to deteriorate.

Wednesday 26 April 2000 - Critical Event 18

- Daughter contacts Cambridgeshire Health Authority Complaints Department

Sunday 30 April 2000 - Critical Event 19

- The patient dies. Death certificates show causes of death to have been
  - Gastrointestinal haemorrhage
  - Pancytopaenia
  - Methotrexate toxicity

11 ACTIONS ALREADY TAKEN

11.1 In response to this incident, parties involved have already instituted a number of changes that the Panel support. These are listed below.

11.2 ***General Practice***

i A meeting was immediately called to discuss events leading to the patient's death.

ii A search was done on the computer to see which patients were on Methotrexate (or drugs of similar toxicity) to check the accuracy of the dosage.

iii When a GP goes on a home visit, they now take a printout of the patient's medication.

iv Warning stickers have been attached to notes alerting staff and GP to patients on specified drugs.

v The GP Practice has upgraded its computer system which has enabled them to add a warning facility to alert the user if a drug dosage is added inappropriately.

vi If a hospital doctors telephones from any hospital with a medication query of any kind they are now automatically put through to speak to a GP and all staff have been made aware at a meeting that this is now practice policy.

11.3 ***Pharmacy***

i A warning card has been circulated to all branches as a reminder that Methotrexate is usually a weekly dose.

ii The computer system has been modified to indicate that Methotrexate is usually a weekly dose.

iii A bulletin has been sent to all branches regarding Methotrexate dosage.

11.4 ***Hospital***

The following actions have been taken or are in the process of being taken with regard to this.

i The induction programme for SHOs will be reviewed with a view to ensuring that the importance of junior staff familiarising themselves with drugs before prescribing is emphasised, including the re-affirmation of the importance of the use of the BNF. This will include raising awareness of the pharmacy advice and information line for staff. A check will be made of all wards to ensure the availability of BNF books. The BNF is already available on the hospital's internal intranet.

ii The Chief Pharmacist will review the policy regarding the use of patient's own drugs, with the recommendation that there will be a list of drugs which are not to be included. The Trust's Drug and Therapeutic Committee has reviewed the hospital "Patient's Own Drugs Procedure". Specific exclusions to use of patients own drugs (all chemotherapy, warfarin, azathiopine) without confirmation (pharmacist or written/ shared care records) have been agreed.

iii The written procedures for pharmacists working at ward level and providing a clinical pharmacy screen of prescriptions received in the dispensary have been revised. The changes reflect the need for discussion between pharmacist and the doctor about any intervention/contribution by a pharmacist which has a major significance or is potentially life saving.

iv The pharmacist will complete an incident form.

v Consideration will be given to pharmacists making an entry in the medical notes. Further discussions are required before this becomes routine practice. Pharmacists are currently advised that, if appropriate, they may make an entry in the medical notes (only after confirmation by a senior pharmacist).

vi The Chief Pharmacist will consider whether there is a need for follow-up action on behalf of the pharmacy department to ensure that recommendations/ alerts made by that department are acted upon appropriately.

vii An awareness exercise to emphasise the need to ensure the proper procedure in the event of incorrect prescribing will be undertaken by senior nursing staff in all areas.

viii Timetables have been amended to ensure that a consultant is available to attend the daily ward round.

12 RECOMMENDATIONS

12.1 It is essential that, in light of this tragedy, all NHS organisations within the Cambridgeshire health system learn from the errors made and put in place mechanisms to minimise the risk of any future occurrences.

12.2 Taking into account all the information gathered by the Panel during the inquiry, the following recommendations for change are made. The recommendations are made in sequence and linked to the chronology of critical events. Wherever possible, specific responsibilities for action have been identified.

Recommendation 1

(January 1997). Shared care arrangements need to include a process whereby the patient, and if appropriate their carer, have suitable time for the health care professional to explain the therapy and answer any questions. In addition, support materials such as patient information sheets should be provided and this should be documented in the medical records.

- Action: Hospital trusts and specialist teams

Recommendation 2

(January 2000). If a patient is admitted to hospital for any form of treatment, the professionals should exercise caution when varying chronic disease management arrangements which are being managed by specialist colleagues and/or the patient's GP. If variations in therapy are recommended then these need to be properly documented and communicated to those managing the shared care arrangements. It is important that there is sufficient time for the health care professional to explain changes in therapy and answer any patient and/or carer questions, which should be documented.

- Action: Trusts to incorporate this into good practice induction/guidelines for junior doctors and nursing staff

Recommendation 3

(6 April 2000). Clinicians need to be cautious when modifying dosages of potentially toxic drugs such as Methotrexate used by older patients. Decisions of this kind should not be rushed and adequate time should be given to ensure the patient and/or their carers understand the changes and are able to ask questions. Any change in therapy including dosage needs to be recorded in both the patient's medical record and computer based prescribing systems held by the GP. Others in the shared care arrangement need to be made aware of the changes.

- Action: Junior doctors, locum GPs and those in medical training programmes need training on the importance of sound communication and the importance of keeping both the patient's medical records and computer based records up-to-date.

Recommendation 4

(6 April 2000). For drugs such as Methotrexate, written prescriptions need to be explicit. Use of phrases such as `as directed` should not be used.

- Action: All prescribers

Recommendation 5

(6 April 2000). Any change in therapy including dosage needs to be recorded in both the patient's medical record and computer-based prescribing systems held by the GP. Clinicians need to be cautious when modifying dosages of potentially toxic drugs such as Methotrexate used by older patients. Decisions of this kind should not be rushed and adequate time should be given to ensure the patient and/or their carers understand the changes and are able to ask questions. Others in the shared care arrangement need to be made aware of the changes.

- Action: Junior doctors, GP locums and those in training programmes need training on the importance of sound communication. Explicit practice systems need to be in place to ensure both written and computer based records are kept up to date.

Recommendation 6

(6 April 2000). GP prescribing software systems need to be programmed to display a warning prompt to prescribers for these potentially toxic drugs to minimise the risk that they are prescribed in error. In the case of Methotrexate the warning prompt should indicate that it is a weekly dose for the treatment of rheumatoid arthritis, and require the prescriber to take specific actions to over-ride the warning.

- Action: GP systems need to be programmed to have specific prompts and secure systems to reduce risk of errors.

Recommendation 7

(6 April 2000). Labelling software within a community pharmacist's premises also needs to have safety protocols which would warn the pharmacist that Methotrexate is usually a weekly dose. Again, the warning prompt should require specific actions by the pharmacist to over-ride the warning.

- Action: Community Pharmacy labelling software needs to have suitable safety prompts and be programmed to reduce likelihood of daily/weekly dosage labelling errors.

Recommendation 8

(6 April 2000) Continuing professional development (CPD) of all professionals including locums is essential to ensure that as a professional they keep abreast of the latest developments and best practice in their field of care. The Panel observes that CPD for locum professionals can be more difficult given the temporary nature of their positions. It is essential that locums take responsibility for their own CPD and keep a record of their CPD activities.

- Action: The CPD of locums needs to be part of the employment policy of the pharmacy and general practice with individual review as an integral part of the policy.

Recommendation 9

(7 April 2000). In any shared care arrangements for chronic disease management the patient and carer responsibilities need to be established so that their role in ensuring the correct administration of medication is explicit. Community pharmacists need to use their prescription records for individuals to check dosage and drug regime with patients or carers collecting medication. If there is a change to the drug regime the pharmacist should check the patient/carer understands the change and what they need to do as a result of this.

- Action: shared care arrangements need to involve training of carers/patients and the shared responsibilities made explicit. Shared care protocols/guidelines and patient held records are an important manifestation of this. Community Pharmacy records of regular customers need to be used to check changes in dosage. Good practice involves discussing and checking with patients and/or their carers their understanding of any changes of dosage or medication.

Recommendation 10

(12 April 2000). Prescribing systems within primary care need to be robust to ensure that that doctors signing repeat prescriptions have access to important information including medical records, and have the time set aside to carry out this task effectively. Any amendments or changes made by the prescribing doctor need to be entered in both the medical and computer records. The use of 'post-it' notes for amending errors in therapy is unreliable.

- Action: the authorising of repeat prescriptions in general practice needs to have the time to make it a clinically sound process with suitable access to necessary records for the signer and ensuring changes are recorded in both notes and prescription systems, including the computer memory.

Recommendation 11

(12 April 2000) Guidance over the deletion from practice computer systems of wrong prescriptions is imperative to ensure systems do not retain wrong prescriptions which could be referenced in the future and possibly lead to the re-issue of an incorrect script.

- Action: GP practices to introduce practice procedures to prevent possible re-issue of an incorrect prescription as a result of incorrect computer files.

Recommendation 12

(12 April 2000) The frequency of repeat prescriptions should be addressed. In this incident, the patient received the new prescription on 6 April and placed a repeat prescription request on 12 April, just six days later. The Panel recommends that such requests should be declined as it encourages individuals to `stock pile` medication.

- Action: GPs and pharmacists to work together to agree what would be a reasonable time lapse before a request for repeat prescription is authorised.

Recommendation 13

(13 April 2000). Shared care arrangements for chronic disease management benefit from patient held records. This can be used by visiting clinicians who may not have immediate access to the medical record. In addition, these booklets could contain useful reminders to patients and their carers about important side effects of these potentially toxic drugs.

- Action: hospital specialists who initiate shared care therapies need to ensure that patient held records are supplied and their role explained. GPs and nurses need to check that they are used and presented at consultations. Periodic checks are necessary over time. Hospital Trusts to revise booklets to include reminders about important side effects.

Recommendation 14

(14 April 2000). Within general practice there needs to be discipline in recording current drug treatments in the prescribing software as well as the medical record if

they are separate. In addition this medical record should have prominent prompts reminding clinicians that the individual patient is on a potentially toxic drug that might interact with new therapies, and list the potential side effects.

- Action: Hospital and GP records need to have visible prompts for patients on potentially toxic drugs.

Recommendation 15

(15 April 2000). Increasingly patients may be visited by or see a doctor out of hours who will not have immediate access to the patient's medical record. This means that patients and their carers will increasingly have more responsibility for relating medical history and current therapies. In addition, the out of hours medical and nursing services need to consider how best to develop electronic links and other support systems to reduce inherent risks.

- Action: GPs need to ensure that patients with chronic diseases have access to patient held records to assist visiting clinicians and community pharmacists. Out of hours co-operatives also need to promote this as a risk management policy.

Recommendation 16

(18 April 2000). When a patient is admitted to hospital it is very important for the referring doctor to ensure that an adequate past medical history and current drug regime is communicated securely to the receiving hospital.

- Action: GP training in this and audit of referral letters is recommended. Trust clinical audit programmes need to follow up the adequacy of clerking of admissions including the physical examination and diagnostic process.

Recommendation 17

(18 April 2000). Emergency referral of older patients with undifferentiated medical problems to a specialist ward should be avoided. We note that this patient had no previous ENT history and the diagnosis of pharyngitis due to infection was tentative.

- Action: Trust admission procedures should be reviewed to encourage the use of medical admissions units for older people with undifferentiated diagnostic problems with onward referral to a specialist ward if this is deemed necessary. Communication of the procedures to all GPs referring to the hospital to inform appropriate GP referral is important. The Trust procedure should include advice to GPs if suggested referral unit is not felt by the hospital doctor to be the most appropriate.

Recommendation 18

(18 April 2000). Systems for accepting patients' own drugs (PODs) needs review so that some potentially toxic and relatively uncommon therapies are subject to closer review by hospital doctors and pharmacists.

- Action: The Trust needs to implement its new policy on PODs so that specified drugs are scrutinised by pharmacists before administration.

Recommendation 19

(18 April 2000). Ward systems need to be more secure so that in the event of a blood sample being reported as inadequate by the receiving laboratory a repeat sample is sent in a timely manner. Ward rounds need to be documented in the medical notes and should include a review of investigation results.

- Action: Trusts need to develop more robust systems to follow up resupply of inadequate samples for testing and improve the rigour of daily ward rounds.

Recommendation 20

(19 April 2000). Prescription errors when noted by doctors, nurses or patients need to be corrected speedily to reduce any risk of perpetuation of dosage errors. 'Post it' notes should not be used to record changes needed to a patient's drug chart. Ward rounds need to be documented in the medical notes and should include a review of drug therapies.

- Action: Trusts should stop using post it notes as a vehicle for communicating changes in therapies and ensure that there is greater sharing of nursing reports at medical ward rounds, which should include a review of drug charts.

Recommendation 21

(20 April 2000). Queries from hospital pharmacists about prescribing errors need to be communicated directly to the prescriber or their deputy and not via a nurse. It is good practice for all wards to have ward pharmacists who can develop relationships with ward personnel, influence good prescribing/administration of drugs procedures and be a daily resource to ward staff. Systems for out of hours and weekends need to be in place.

- Action: Trusts should consider providing ward based pharmacists for all wards and secure systems for out of hours. Procedures should be reviewed to ensure that any significant queries from the hospital pharmacist regarding prescribed drugs are communicated directly with the prescriber.

Recommendation 22

(20 April 2000) If a hospital doctor needs to check a patient's prescription with a GP prescriber, for toxic drugs such as Methotrexate, confirmation of prescription should be sought directly from the prescriber.

- Action: Trust to identify such drugs and introduce a procedure to support this.

Recommendation 23

(21 April 2000). If a patient's condition is not improving as anticipated on the admission assessment then a thorough review needs to be undertaken and consultant involvement sought. Drug side effects need to be more prominent in junior doctor training and considered as a possibility in those with chronic diseases on multiple drug therapies.

- Action: Review of patient's progress in daily ward rounds needs to be made against admission diagnosis and early involvement by consultant staff in the event of deterioration or lack of progress. Those responsible for clinical training, including the training of junior doctors, which should provide training on drugs and their side effects.

Recommendation 24

(22 April 2000). Nurses are important members of ward teams. The nursing records need to form part of ward rounds so that concerns about the possible diagnosis or therapies are shared explicitly with the clinical team.

- Action: Trust processes need to be reviewed to ensure nurse records and observations are considered at daily ward rounds.

Recommendation 25

Awareness of the drug Methotrexate and associated risks need to be raised across the NHS nationally. Lessons from this Inquiry should be shared.

- Action: Cambridgeshire Health Authority to request a national communication to be co-ordinated by the Department of Health. The report will be posted on the Cambridgeshire Health Authority website and all health authorities will be alerted to this report on the site and its significance.

Recommendation 26

Recognised sources for drug information such as the BNF need to be reviewed to ensure that the potential toxicity of Methotrexate is highlighted in the context of its increasing use in chronic disease management. These information sources should also reinforce the use of Methotrexate in these conditions as a weekly rather than daily regime.

- Action: Cambridgeshire Health Authority to communicate the findings of this Inquiry to the Department of Health, BNF, MIMMS and to the Pharmaceutical industry.

Recommendation 27

Drug companies who have licenses for the use of Methotrexate in psoriasis and rheumatoid arthritis, should review their packaging for Methotrexate so that it reinforces to pharmacists, doctors and patients in a community setting that this is a weekly dose. The tablets should be available in blister packs with warnings that this is a weekly dose.

- Action: Cambridgeshire Health Authority to approach the Department of Health and Medicines Control Agency about these issues.

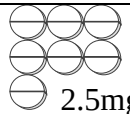
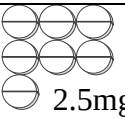
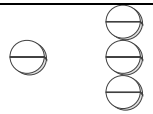
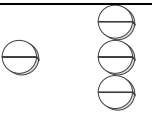
Recommendation 28

The appearance of the Methotrexate tablets should be reviewed in order to assist with identification of the strength of each tablet. The similarity between the 2.5mg and 10mg tablets presents a risk when handling such potentially toxic drugs. It is questionable if the 10 mg tablets need to be available in the community. Drug companies should review their patient information leaflets contained in Methotrexate packs to take account of its increasing use in the treatment of rheumatoid arthritis. The inclusion of a number of leaflets in each pack would provide pharmacists with a supply to distribute to patients.

- Action: Cambridgeshire Health Authority to approach the Department of Health and Medicines Control Agency about these issues.

APPENDIX 1

PATIENT'S METHOTREXATE DOSE AND REGIME

	SUN	MON	TUE	WED	THURS	FRI	SAT	SUN
Usual dosage regime 17.5mg weekly **Total weekly dose 17.5 mg**	 2.5mg							 2.5mg
Intended change to regime: 1 x 10mg tablet to be supplemented with 3 x 2.5mg tablets from patient's current supply weekly **Total weekly dose 17.5 mg**	 10mg 2.5mg							 10mg 2.5mg
Actual resulting regime **Total weekly dose 70 mg**	 10mg	 10mg	 10mg	 10mg	 10mg	 10mg	 10mg	 10mg

Key

 2.5 mg light yellow tablet – scored M2.5

 10 mg darker yellow tablet – scored M10

APPENDIX 2

SERIOUS UNTOWARD INCIDENT PROCEDURE

NHS EXECUTIVE

" A serious untoward incident to be reported under this procedure is any incident on an NHS site or elsewhere whilst in NHS-funded or NHS regulated care involving:

a) NHS patients, relatives, visitors;
b) staff, students undertaking clinical or work experience and/or their tutors;
c) contractors, equipment, buildings or property,

and which:

- caused death (including suicide) or serious injury or was life-threatening;
- contributes to a pattern of a sustained fall in standards of care;
- involved a hazard to public health, including major toxic contamination or radiation hazard;
- involved the absconding of a detained mental health patient;
- caused serious disruption to services;
- caused significant damage to the assets of an NHS organisation;
- may cause significant damage to the reputation of an NHS organisation or its staff;
- involved fraud or suspected fraud (the procedure in HSC 1999/062 must also be observed in parallel);
- may or did give rise to a significant claim for damages or to legal proceedings;
- involved the suspension of a member of clinical staff or a student on clinical grounds or for reasons associated with patient care;
- causes concern following an inquest;
- may create adverse media coverage of potential regional or national interest

It is recognised that a degree of judgement is required when deciding when to report an incident. If in doubt, please seek the advice of your local Health Authority communications team or the Regional Office."

APPENDIX 3

INQUIRY PANEL MEMBERSHIP

Panel Chairman: Owen Ingram, Non Executive Director, Cambridgeshire Health Authority
Owen Ingram has been a non-executive Director of various health authorities in Cambridgeshire, including the Family Health Service Authority, and a vice chair of South Peterborough Primary Care Group. He works as Management Consultant working with mental health and special needs groups. Prior to this he was Chief Executive of the Richmond Fellowship and a number of other national charities.

Dr Ian Dumbelton, General Practitioner
Dr Dumbelton has been a General Practitioner in St Neots since 1984. He has been a member of the Local Medical Committee (LMC) for six years and LMC Chair for 2½ years. He has taken an active role in the discipline and poor performing procedures for General Practitioners locally.

Tim Coaker, Community Pharmacist
Tim Coaker has worked in and around Cambridgeshire for the last 20 years as a Community Pharmacist/Manager in various Boots the Chemists stores. Currently manager of the Boots the Chemist store in Bretton, Peterborough, Tim was formerly vice chairman of the former North West Anglia Local Pharmaceutical Committee, and has been Chairman of the Cambridgeshire Local Pharmaceutical Committee since April 1999.

Dr Nicholas Sheehan, Consultant Rheumatologist, Peterborough Hospitals NHS Trust
Dr Sheehan has been a Consultant Rheumatologist since 1986. He is Chairman of the East Anglian Society for Rheumatology and a Regional Advisor in Rheumatology to the Royal College of Physicians. He is President Elect of the Rheumatology and Rehabilitation Section of the Royal Society of Medicine, Honorary Treasurer of the British League Against Rheumatism and a former member of the Executive of the British Society for Rheumatology.

Dr Tony Jewell, Director of Public Health, Cambridgeshire Health Authority
Tony Jewell has been a Director of Public Health for 5 years and a Public Health Doctor for 10 years. Before training in Public Health he was a principal in general practice for 10 years.

Administrative support was provided by Andrea Prime, Head of Corporate Services and Nicky Hallows, Complaints Officer, Cambridgeshire Health Authority:

Andrea Prime, Head of Corporate Services, Cambridgeshire Health Authority
Andrea Prime has an administrative background of eight years, with four years' experience in the NHS. Andrea Prime is Head of Corporate Services for the Cambridgeshire Health Authority and in this role oversees the management of complaints and legal proceedings for the Authority.

Nicky Hallows, Complaints Officer, Cambridgeshire Health Authority
Nicola Hallows has a background in teaching and for the past seven years has worked for the Health Authority complaints department, responsible for family health services complaints handling and disciplinary procedures.

APPENDIX 4

MEETINGS OF THE PANEL

The Inquiry Panel met on four occasions: 6 June, 15 June, 27 June and 10 July. This report was prepared by the Panel using information and observations gleaned from all of the sources listed in Appendix 5.

Date	Task	Hours
6 June	Designed process for Inquiry	2
15 June	Reviewed evidence from parties and identified further information requirements	4
27 June	Interviews with parties involved plus analysis of further written information	8
10 July	Review summary report of interview. Considered further information obtained and formed structure of report	4

In addition, panel members made further investigations including discussions with a number of people, visits to the GP practice and the pharmacy and scrutiny of medical records from the hospital and GP settings.

APPENDIX 5

SOURCES OF INFORMATION FOR THE INQUIRY PANEL

a)	*Written statements by*: The family The General Practice and the GP within this practice The Community Pharmacy The Hospital
b)	*Interviews held by the Panel with*: Family member representatives – 6 General Practice representatives – 5 Community Pharmacy representatives – 3 Hospital representatives - 7
c)	*Case notes and monitoring charts for the patient from the General Practice, Pharmacy and Hospital*
d)	*Policies and procedures relevant to system failures within the General Practice, Pharmacy and Hospital*
e)	*Background literature on Methotrexate and other untoward incidents causing either death, serious injury or life threatening circumstances caused by Methotrexate*

THE BRITISH SOCIETY FOR RHEUMATOLOGY

GUIDELINES FOR SECOND LINE DRUG MONITORING

Methotrexate

A typical dose regimen may be:- 7.5mg weekly increasing by 2.5 mg every 6 weeks to 15-20mg weekly as appropriate. Lower doses should be used in the frail elderly or if there is significant renal impairment. Folic acid 5mg given 3 days after each dose may reduce the incidence of toxicity. Care must be taken to avoid cotrimoxazole in patients taking Methotrexate.

Typical pretreatment assessment:- FBC, U&E's, LFT's (incl. AST or ALT), Chest X-ray.

Typical monitoring:- FBC weekly unti1 6 weeks after last dose increase and provided it is stable monthly thereafter. LFT's (incl. AST or ALT) 2-4 monthly. U&E's 6-12 monthly (more frequently if there is any reason to suspect deteriorating renal function).

Action to be taken:-

WBC<4.0x10^9/1	withhold and discuss with rheumatologist
neutrophils<2.0x10^9/1	withhold and discuss with rheumatologist
platelets<150x10^9/1	withhold and discuss with rheumatologist
>2-fold rise in AST, ALT or Alk. Phos	withhold and discuss with rheumatologist
unexplained fall in albumin	withhold and discuss with rheumatologist
rash or oral ulceration	withhold and discuss with rheumatologist
new or increasing dyspnoea	withhold and discuss with rheumatologist
MCB>105fl	check B12 & folate and if low start appropriate supplementation
significant deterioration in renal function	reduce dose
Abnormal bruising or sore throat	withhold until FBC result available

Please note that in addition to absolute values for haematological indices a rapid fall or consistent downward trend in any values should prompt caution and extra vigilance.

Extract from the British Society for Rheumatology
Guidelines for Second Line Drug Monitoring

APPENDIX 7

GUIDELINES FOR THE USE OF METHOTREXATE IN RHEUMATIC DISEASES

AIMS

Methotrexate is used as a disease modifying agent to induce and maintain a remission of rheumatoid arthritis. It is potentially toxic and therefore the drug must be monitored. Doses should be lowered in patients with impaired renal function.

DOSAGE

1. Start with 7.5 mg, orally or im, or subcutaneously **ONCE PER WEEK**.
2. According to clinical response, this weekly dosage may be increased by increments of 2.5-5.0 mg, at intervals of four weeks, to a maximum dosage of 25 mg. **ONCE PER WEEK.**
3. **INCREASING THE DOSE ABOVE 15 MG, SHOULD ONLY BE DONE AFTER DISCUSSION WITH THE HOSPITAL CONSULTANT CONCERNED.**
4. Clinical response usual at 4-6 weeks.

MAIN SIDE EFFECTS

1. **Common**: Nausea, anorexia, oral ulceration, minor hair thinning, abdominal discomfort, diarrhoea, headaches.
2. **Less common**: Rash, bone marrow suppression, causing thrombocytopenia, neutropenia and rarely anaemia.
3. **Rare but important: a) Hepato-toxicity**. Rarely Methotrexate may cause liver fibrosis/cirrhosis. Where alcohol is avoided this has proven rare. Avoid if pre-existing liver disease. **b) Pulmonary toxicity** .Acute pneumonitis or chronic pulmonary fibrosis may occur. This is not dose related. It presents with dry cough, dyspnoea and often fever. Pre-treatment CXR is recommended.
4. Methotrexate is teratogenic to ova and sperm. Therefore patients of either sex should be counselled about contraception, during treatment and for 3 months after stopping Methotrexate.
5. Close contact with chicken pox or shingles -non immune patients require Acyclovir.

MONITORING

1. FBC & LFT's fortnightly for the first 4 weeks and thereafter monthly. ESR monthly to help assess response to treatment. Look out for downward trends as well as absolute levels of blood cell count.
2. Record results in patient held booklet.

SIDE EFFECTS AND WHAT TO DO

1. Nausea, abdominal discomfort, diarrhoea and anorexia may be helped by the addition of folic acid 5 mg, twice/week.

2	**WBC< 3,500/mm^3**	)	
3	**Platelets< 150/000/mm^3**	)	**STOP** Methotrexate and inform
4	**ALT> twice upper limit of normal**	)	Rheumatologist or Nurse
	or falling albumin	)	Practitioner
5	**Symptoms of pneumonitis**	)	

DRUG INTERACTIONS

Never prescribe TRIMETHOPRIM or SEPTRIN. Caution with anticonvulsants. Avoid live vaccines. There are no contra-indications in using NSAID's with the doses of Methotrexate that we prescribe.

GLOSSARY OF TERMS

Blister pack – a pack of tablets where each one is separately sealed inside a plastic covering
BNF – British National Formulary – a pocket book for those concerned with the prescribing, dispensing and administration of medicines in Britain, produced jointly by the Royal Pharmaceutical Society and the British Medical Association.
Care pathway – the overall pattern of care and all those involved in delivering it to a patient
Chronic disease – a persistent or recurring condition. The disease, which may or may not be severe, often starts gradually and changes will be slow.
Community pharmacist – the high-street pharmacist (chemist)
Dosage – the amount and frequency of a drug
ENT- Ear, nose and throat
General practitioner (GP) - a doctor who, often with colleagues in partnership, works from a local surgery providing medical advice and treatment to patients who have registered on his list. The doctor is almost always supported by practice nurses, with other specialist nurses based at his surgery and working among his patients. A GP is not usually employed by the NHS, but provides services to patients through a contract with the Health Service.
Immunosuppressant – the therapeutic suppression of the body's defences. The prevention of organ rejection by recipients of kidney, heart and bone-marrow transplants is the most clear-cut application.
Junior doctors - doctors do the final years of their training in hospitals. They start as house officers, become senior house officers (SHOs), and then specialist registrars (SpRs). During this time they become increasingly specialised and qualified, until they are appointed to senior consultant posts.
MIMS – Monthly Index of Medical Specialties.
Penicillamine – a derivative of penicillin, sometimes used in rheumatoid arthritis that has not responded to the first-line remedies.
Psoriasis is a skin disease. It presents as raised red patches of skin which may occur anywhere on the body and are covered by silvery scales. However, common sites are the knees, elbows and the scalp. Small areas of the skin are generally affected, but in some rare cases there may be a widespread serious eruption.
Regime- a course of treatment
Results booklet – a booklet held by the patient which records results of tests.
Rheumatoid arthritis (RA) Is a chronic disease affecting joints. The problems are primarily a consequence of persistent inflammation which is part of the body's defence mechanism for dealing with infections for example. In RA, however, the inflammation in joints becomes persistent and damages them. Whilst any joint can be affected, it is usually in the small peripheral joints, such as those in the fingers or wrist, that this is first noticed. Often, joints are affected symmetrically. Although RA usually begins to affect people from their forties onwards, it can strike at any age, including young children.
Shared care arrangements – arrangements for therapy made between hospital specialists, general practitioners and the patient.
SHO (Senior House Officer) – see Junior doctors
SpRs (Specialist Registrar)– see Junior doctors
Stock drug – drugs normally kept in hospital or ward.
Toxic – all drugs are potentially toxic but some such as Methotrexate need to be used with special care.
Ward pharmacy – a hospital pharmacist who visits the ward regularly.