MEETING

JOINT HEALTH OVERVIEW AND SCRUTINY COMMITTEE

DATE AND TIME

FRIDAY 27TH NOVEMBER, 2015

AT 10.00 AM

VENUE

HENDON TOWN HALL, THE BURROUGHS, LONDON NW4 4BQ

Dear Councillors,

Please find enclosed additional papers relating to the following items for the above mentioned meeting which were not available at the time of collation of the agenda.

Item No	Title of Report	Pages
1.	AGENDA AND REPORT PACK	1 - 188

Rob Mack, London Borough of Haringey 020 8489 2921 Email: rob.mack@haringey.gov.uk

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AGENDA ITEM 1

JOINT HEALTH OVERVIEW AND SCRUTINY COMMITTEE

Barnet, Haringey, Camden, Islington and Enfield

Friday 27 November at 10:00 a.m.

at

Barnet Town Hall, the Burroughs, Hendon, NW4 2ER

27 November 2015

DEPUTATION STATEMENT

on behalf of the patients of the LUTS Clinic, Whittington Health

(submitted 18 November 2015)

Dear members of the Joint Health Overview and Scrutiny Committee

PATIENT PLEA – A LETTER TO THE JHOSC

Please accept our most sincere thanks to you for agreeing to this Deputation from the Patients of the LUTS Clinic. We understand that many, if not all of you, are already aware of the subject matter of this Deputation submission, being the closure of the LUTS Clinic and prevention of appropriate and effective treatment for Patients of the LUTS Clinic who all suffer from chronic, intracellular bacterial infection of the urinary tract and bladder.

We wish to impress upon you the profound effect the closure of the LUTS Clinic has had on patients (approximately 40% of whom reside within your respective constituencies) and on Professor James Malone-Lee and his team at the LUTS Clinic.

The closure of the LUTS Clinic jeopardises the reputation and legacy of an extraordinary clinician and exceptionally caring human being. Professor Malone-Lee has been the very definition of salvation for each and every patient who has been fortunate enough to be in his care. It has taken many of us, years to find him. Professor Malone-Lee's tireless efforts to understand our illness and his indisputable success in controlling and curing our chronic, intracellular bacterial infection of the urinary tract and bladder should be a source of pride for your respective boroughs.

Rest assured, the debt of gratitude we all owe to Professor Malone-Lee would, of itself, have brought us to your door.

Unfortunately, the closure of the LUTS Clinic has a much more damaging and dangerous impact which must be the focus of this Deputation.

The closure of the LUTS Clinic has effectively given a prison sentence to each and every one of Professor Malone-Lee's 900+ current, and undoubtedly thousands of future, patients. The vast majority of patients are women, however there are still a significant number of men who are no less affected by this condition.

Our condition: a chronic, intracellular bacterial infection of the urinary tract and bladder:

(a) **is painful:** excruciating pain in the urethra, vagina, bladder, pelvis, kidneys, abdomen and legs. Burning urination, blood in the urine, intense pressure in the bladder, pelvic and bladder spasms.

(b) **is debilitating:** pain, nausea, fatigue, anxiety, panic attacks and depression leading to an inability sleep, to concentrate, to work, to exercise, to experience intimacy and to care for families;

(c) **is humiliating**: urinary incontinence; constant need to be using or near a toilet; being patronised and derided by medical staff (outside of the LUTS Clinic) who believe we have created our symptoms just to get attention;

(d) **is dangerous:** kidney infections, prostatitis (in men) kidney failure and sepsis (blood poisoning) and ultimately the risk of death.

If left untreated or if inappropriately treated, it can be severely damaging to our bodies, our minds, and ultimately our lives. If, as a result of this Deputation, you understand even a fraction of the suffering and damage caused by our condition, we are confident you will support our requests as best you can. The treatment we receive at the LUTs Clinic, while it

can be lengthy, ultimately cures our condition and in the meantime reduces our symptoms to a manageable level to enable us to live and enjoy our lives.

We regret that we have very little evidence of the factual circumstances surrounding the closure of the LUTS Clinic. We have tried many avenues to obtain documentation, reports, impact assessments etc, from Whittington Health including through Freedom of Information requests and even direct appeals to the Medical Director, Dr Richard Jennings, himself. Unfortunately we have not yet received much of anything. We have therefore attempted to restrict this Deputation to those matters of which we have been directly informed. However, we are compelled to state that, as a patient collective, we are growing increasingly concerned each day as to the lack of information received from Dr Jennings and Whittington Health and that we are given ever growing cause to question the adherence to their Duty of Candour[1] in relation to the information and communications we have received to date.

If you have any questions when considering this Deputation please contact Holly Boyd (a LUTS Clinic patient) on 07747309192 or holly.s.boyd@hotmail.com (day or night) who will co-ordinate efforts to provide you with what you need.

With kind regards
Patients of the LUTS Clinic

[1] The Duty of Candour (including openness and transparency) is a fundamental standard which applies to health service bodies pursuant to the Health and Social Care (Regulated Activities) Regulations 2014.

1. Executive Summary

This Deputation is being submitted to the JHOSC on behalf of the Patients of the LUTS Clinic, in relation to the Closure of the LUTS Clinic.

The Patients request that the members of the JHOSC exercise their relevant functions pursuant to the Local Authority (Overview and Scrutiny Committees Health Scrutiny Functions) Regulations 2002, to:

(a) **review** and **scrutinise** the circumstances leading to, and the final decision to issue, the Clinical Restriction to Standard Guidelines, taking into account;

(i) that the consultation carried out by Dr Jennings and Whittington Health was non-existent and therefore wholly inadequate (as set out in Section 0 (*Failure to consult; no assessment of Patient clinical history; no assessment of risks to Patients*));

(ii) that no sustainable service improvement will be delivered as a result of the Clinical Restriction to Standard Guidelines (as set out in Section 6 (*the Clinical Restriction to Standard Guidelines provides no service improvement*));

(iii) that the Clinical Restriction to Standard Guidelines has led to serious healthcare inequalities, (as set out in Section 7 (*Creation of healthcare inequalities*)); and

(iv) the profoundly adverse impact on Patients as a result of the Closure of the LUTS Clinic (as set out in Section 8 (*Impact on patients*);

(b) **report** and **make recommendations** to both Whittington Health and the Secretary of State for Health for:

(i) the immediate withdrawal of the Clinical Restriction to Standard Guidelines (as set out in Section **Error! Reference source not found.** (*Patient goals*);

(ii) a more appropriate and proportionate response to the Patient Incident which takes into consideration the safety of Patients at risk of a similar Patient Incident but which does not adversely affect the treatment of other Patients (as discussed and set out in the final paragraph of Section 5 (*Failure to consult; no assessment of Patient clinical history; no assessment of risks to Patients*)); and

(iii) the recognition of Chronic Intracellular Bacterial UTI as a chronic form condition distinct from the acute or recurrent form of cystitis, urinary tract infection or UTI and the support and the development of PML's research and PML's Treatment Protocol (as set out in Section **Error! Reference source not found.** (*Patient goals*)), including appropriate succession arrangements, to ensure effective treatment for future sufferers; and

(c) to use the joint powers of the JHOSC to **refer** the decision to impose the Clinical Restriction to Standard Guidelines (and the circumstances surrounding such restriction) to the **Secretary of State for Health** for his consideration pursuant to section 25 (*Decisions and directions by Secretary of State or the Board*) of the Local Authority (Public Health, Health and Wellbeing Boards and Health Scrutiny) Regulations 2013 (or otherwise).

With respect to the requests contained in this Section, the Patients further request that the JHOSC consider and address the breaches of the NHS Constitution and the Human Rights Act 1998 as set out in Section 9 (*Breaches of the NHS Constitution and Human Rights Act*).

2. Definitions

Defined terms in this Deputation have the following meaning:

12 November Trust Meeting means the meeting held by Whittington Health on 12 November 2015, with attendance by (among others) Dr Jennings and Simon Pleydell, Chief Executive of Whittington Health and approximately 120 Patients (plus family and carers). Minutes of this meeting, as provided by Whittington Health are **attached** as **Appendix A**.

Chronic Intracellular Bacterial UTI is what the Patients of the LUTS Clinic suffer from, which is a chronic, intracellular or biofilm bacterial infection of the urinary tract and bladder (also sometimes called chronic cystitis or chronic UTI).

Clinical Restriction to Standard Guidelines has the meaning as described in Section 3 (*Clarification of the closure of the LUTS Clinic*).

Closure of the LUTS Clinic has the meaning as described in Section 3 (*Clarification of the closure of the LUTS Clinic*).

COBF Forum means the post to the Cystitis and Overactive Bladder Foundation Forum, located at: http://cobf.websitetoolbox.com/post/a-message-regarding-the-clinic-of professor-ml-7766407?&trail=105

JHOSC means the Joint Health Overview and Scrutiny Committee comprised of the Chairmen of the Health Overview and Scrutiny Committees from the five London boroughs of Barnet, Haringey, Camden, Islington and Enfield, meeting on 27 November 2015.

LUTS Clinic means the Lower Urinary Tract Service, Hornsey Central Neighbourhood Health Centre run by Whittington Health (an NHS Trust service), headed by PML.

Mr Pleydell means Mr. Simon Pleydell, Chief Executive of Whittington Health.

NHS Constitution means the NHS Constitution for England, current edition as at 26 March 2013.

Patients means the patients of the LUTS Clinic, of which there are currently 904.

Patient Incident means the Patient incident as described in Section 4 (*the patient incident that lead to the closure of the LUTS Clinic*).

PML means Professor James Malone-Lee MD FRCP.

PML's Treatment Protocol means the November 2014 Protocol for management of patients with chronic lower urinary tract symptoms with clinical evidence of urinary tract infection – Whittington Lower Urinary Tract Symptoms Clinic, Professor James Malone-Lee MD FRCP, and **attached** as **Appendix B**.

Dr Jennings means Dr Richard Jennings, Executive Medical Director of Whittington Health.

3. Clarification as to the closure of the LUTS Clinic

On 21 October 2015, Dr Jennings placed a formal restriction on the clinical practice of PML at the LUTS Clinic (for both NHS and private patients). The restriction stipulated that "*from now onwards, [PML's] antimicrobial prescribing must adhere to the written guidance provided through the extraordinary meeting of the Joint Antimicrobial Steering Group (ASG and Drug & Therapeutics Committee (D&TC) meeting on 4th August 2015...*" (**Clinical Restriction to Standard Guidelines**). This restriction effectively prevents PML and the LUTS Clinic from treating Patients in accordance with PML's Treatment Protocol and instead permits treatment only in accordance with standard guidelines for acute urinary infections. The Letter in which this formal restriction was expressed is **attached** as **Appendix C**.

Through the COBF Forum Post, PML provided the following information to Patients with regard to the Clinical Restriction to Standard Guidelines:

> "*100% of the patients attending [the LUTS Clinic] are referred because they have failed to respond to similar guidelines, repeatedly applied, so it would not be appropriate to institute such treatment again. This means that I am no longer permitted to prescribe alternatives and I have to desist. I very much regret that I must therefore suspend this service until such time as further instructions are provided*."

On 22 October 2015, the Patients received a letter from Dr Jennings that notified them of the suspension of the LUTS Clinic, effective immediately (this Letter is **attached** as **Appendix G**).

At the 12 November Trust Meeting Dr Jennings implied that he could not have foreseen PML's decision to close the LUTS Clinic as a result of the imposition of the Clinical Restriction to Practice:

> "*The intervention was focussed on prescribing practices and not an intervention about closing the clinic. Professor James Malone-Lee – a person the Trust and I have huge respect for – made the decision that he was not able to continue the clinic. Closing the clinic was not a restriction imposed on him by the Trust. This meant we weren't able to put in place the systems we would have wanted in order to fully support patients.*"

The Patients do not accept that PML's decision to suspend the LUTS Clinic can be considered unforeseen, nor that Dr Jennings can claim ignorance as to PML's viewpoint on standard treatments protocols for his Patients. PML has been very clear on this for many years. In a 2013[2] letter (**attached** as **Appendix L**) to Dr Michael Kelsey (Consultant Microbiologist, Chair of the Drug & Therapeutics Committee for Whittington Health and member of the Steering Group who provided Dr Jennings with

[2] The letter from PML was obtained as part of a Freedom of Information Act request. Unfortunately the letter appears to be incorrectly dated as 28 October 2015. Evidence that the correct date of the letter is between 30 June 2013 to 22 January 2014 is contained in the documentation collated at Appendix L. The letter from PML refers to the 30 June 2013 Letter from Dr Kelsey and the Minutes of the LUTS prescribing meeting of 22 January 2014 refers to the receipt of the letter from PML.

the written guidance used as the basis for the Clinical Restriction to Standard Guidance), PML states that:

> "*I should be failing as a doctor if I were to deny such patients treatment because their needs were not covered by guidelines. I am obliged to manage these people, to the best of my ability, using all of the advice and knowledge that is available to me.*"

Given the Clinical Restriction to Standard Guidelines prohibited PML from treating Patients to the best of his ability, using all of the advice and knowledge that was available to him, it is unsurprising that PML was compelled, as a matter of professional ethics and personal integrity, to decline to treat his Patients in accordance with such stipulations and therefore had no choice but to suspend the LUTS Clinic.

Further, it is clear from the letter in which Dr Jennings imposes the formal restriction on PML (**attached** as **Appendix C**), that PML and Dr Jennings had a conversation immediately prior to the formal letter being sent. While we can only speculate, we can be fairly certain that PML would have expressed viewpoint to Dr Jennings in that meeting. Dr Jennings elected to proceed with the formal restriction, regardless.

We wish to clarify that the Patients are in full support of PML's stance to suspend the LUTS Clinic as a result of the Clinical Restriction to Standard Guidelines, as the restriction on his practice would mean his treatment would be inappropriate and ineffective and provide no beneficial service to Patients.

Any reference in this Deputation to the **Closure of the LUTS Clinic** is a reference to its constructive closure as a result of the imposition of the Clinical Restriction to Standard Guidelines, for which Dr Jennings is responsible.

4. The Patient Incident that lead to the Closure of the LUTS Clinic

During the 12 November Trust Meeting, Dr Jennings communicated to the Patients present that the catalyst for the Clinical Restriction to Standard Guidelines was the occurrence of a 'patient incident'. Dr Jennings confirmed that a Patient suffered organ damage as a side effect of Nitrofurantoin (an antibiotic), which the Patient was taking as part of long-term treatment (**Patient Incident**). Unconfirmed by Dr Jennings, but what we understand is that the Patient, who was quite elderly, developed some sort of lung damage.

Dr Jennings confirmed to the Patients present at the 12 November Trust Meeting that his decision to impose the Clinical Restriction to Standard Guidelines was a "*judgement call*" made by him (in consultation with Dr Andy Mitchell, Medical Director for NHS England for London) in reaction to this Patient Incident. We are also of the understanding that a very similar Patient Incident occurred approximately 6 years ago which also was a factor in Dr Jennings' judgement. It was pointed out to Patients at the 12 November Trust Meeting that Dr Jennings was responsible for the judgement call and that Mr Pleydell was not involved.

Unfortunately we do not have any specific details regarding the Patient Incident, nor have we had sight of documentary evidence that the organ damage was caused by

PMLs Treatment Protocol. We wish to highlight that the Patient Incident, together with first incident 6 years ago (of which we have no information), represents an 'incident' ratio of a miniscule 2:900, which is 0.22%. This does not even consider the hundreds, if not thousands, of Patients PML has treated successfully and who are not considered part of his current set of 900+ Patients.

5. Failure to consult; no assessment of Patient clinical history; no assessment of risks to Patients

We confirm that no Patient was consulted with regard to the Clinical Restriction to Standard Guidelines. Very simply, this amounts to a wholly inadequate consultation performed by Dr Jennings and Whittington Health in breach of the NHS Constitution as set out in **Appendix D**.

Additionally it became apparent during the 12 November Trust Meeting that, despite stating he "*certainly assessed the risk of imposing a practice restriction on antimicrobial prescribing in the clinic*", Dr Jennings:

(a) responded disproportionately to an incident affecting one single Patient by imposing the Clinical Restriction to Standard Guidelines, which amounted to wholesale changes to the treatment of 900+ Patients, without even appropriately considering the risks:

> "*When a patient safety event occurs you have to respond immediately to address that risk. We now need to look more closely at the physical and psychological risks to patients*";

(b) had not reviewed one single Patient history or case prior to imposing the Clinical Restriction to Standard Guidelines:

> "*When I made the evaluation about what had happened I did not go through a review of all the histories in the clinic and it would not have been practical to do so.";*

(c) at the point of imposing the Clinical Restriction to Standard Guidelines, had not conducted, or commissioned, a risk assessment for the individual Patient who suffered the Patient Incident:

> "*A Risk assessment for the individual patient who suffered harm will be properly made in an individual investigation which is not conducted by me, and that's the serious incident investigation*."; and

(d) at the point of imposing the Clinical Restriction to Standard Guidelines, had not conducted a risk assessment on the impact and affect such a restriction would have on 900+ Patients:

> "*What we have not anticipated is all the different aspects of complexity that have occurred since the practice restriction on 21 October. The distress that the restriction has caused, the pain that it has caused people and the difficulties we have had in producing a responsive alternative for you were not fully foreseen*".

Further, the Patients understand that only a limited number of the 900+ Patients are currently taking a prolonged course of the alleged offending antibiotic (Nitrofurantoin), with other Patients currently on treatment regimes that do not involve antibiotics at all. Further, the imposition of the Clinical Restriction to Standard Guidelines does not even adequately mitigate the risk of a similar patient harm incident to that of the Patient Incident, as the particular side effect of lung damage can occur even as a result of the short course of Nitrofurantoin (which is advocated in the Clinical Restriction to Standard Guidelines).

The Patients therefore consider the Clinical Restriction to Standard Guidelines to be an entirely inappropriate and disproportionate response to a single patient incident that in fact amounts to negligence and a breach of duty toward all 900+ Patients (including the Patient who suffered the Patient Incident). Additionally, this also amounts to a breach of certain NHS rights and pledges and of Patients' human rights as set out in **Appendix D**.

Proposed recommendations

The Patients recommend that a proper investigation into the Patient Incident be conducted and that a targeted and more appropriate and proportionate response to the safety concerns for that particular Patient and any future similar incident be applied. A more appropriate response may include:

(i) immediate testing of all Patients who were or are taking Nitrofurantoin as part of their treatment regime, so as to identify or rule out any similar harm to Patients' lungs;
(ii) investigation into and imposition of additional monitoring requirements for Patients, especially the elderly, who have been prescribed Nitrofurantoin; and/or
(iii) satisfactory lung tests every three to six months prior to being able to continue the prolonged course of Nitrofurantoin;
(iv) or even a restriction on the prescription of prolonged Nitrofurantoin treatment for the elderly only, unless the benefits appropriately outweigh the risks on a case-by-case basis.

These are just some suggestions that would have been a much more appropriate and proportionate response to the Patient Incident and which would not have introduced such multiple risks and far reaching consequences for all other Patients. We are confident that the appropriate level of additional safety measures for this specific incident type can be achieved without resorting to the type of risky wholesale changes imposed by the Clinical Restriction to Standard Guidelines.

6. The Clinical Restriction to Standard Guidelines provides no service improvement

As mentioned above in Section 3 (*Clarification as to the closure of the LUTS Clinic*), Dr Jennings' Clinical Restriction to Standard Guidelines was based on the written guidance provided through the extraordinary meeting of the Joint Antimicrobial Steering Group (ASG) and Drug & Therapeutics Committee (D&TC) meeting on 4th

August 2015 (**Steering Group**). **Attached,** as **Appendix E**, is a copy of the written guidance provided by the Steering Group.

Dr Jennings stated in the 12 November Trust Meeting that "*the guidelines highlight what the effects and the potential side effects of antibiotics are, as well as the recognised and recommended durations*".

Attached as **Appendix F** is the Summary of Product Characteristic (**SmPC**) for Nitrofurantoin (macrobid capsules, 100mg), which is the reference relied upon by the Steering Group in its 'final recommendation re: Nitrofurantoin' as contained in its written guidance (**Appendix E**). The SmPC states that the posology (the dosage) for Adults, Children over 12 years of age and (provided no significant renal impairment) the Elderly is "100mg twice daily for 7 days". As stated in the SmPC, this posology is the licensed treatment and duration for "acute and recurrent uncomplicated UTI [and pyelitis (inflammation of the renal pelvis)]". What the Steering Group therefore failed to take into account within its written guidance is the fact that there is no posology recommended within the Nitrofurantoin SmPC for Chronic Intracellular Bacterial UTI (or any consideration of a chronic condition).

If you review the SmPC for each of the antibiotics considered by the Steering Group in its written guidance, you will discover the exact same pattern of failure to consider the application of the relevant antibiotic in the context of the chronic condition.

Further, it is evident that the Steering Group did not consider any Patient case history or the fact that all 900+ Patients had been referred to the LUTS Clinic exactly because the standard guidelines have consistently failed them (owing to their condition not being 'actue' and therefore falling outside the consideration of these standard posology guidelines).

Consequently, we submit that it was inappropriate and ultimately negligent for Dr Jennings to base his Clinical Restriction to Standard Guidelines solely on the guidance of the Steering Group's written guidelines, without considering any other external factors, and that such decision did not, and will not, deliver any service improvement to any Patient (quite the contrary, it has delivered a complete service detriment).

7. Creation of healthcare inequalities

The Clinical Restriction to Standard Guidelines and the subsequent Closure of the LUTS Clinic resulted in the creation of profound health care inequalities.

The primary inequality caused by the Closure of the LUTS Clinic is that all 900+ Patients are now subject to:

(a) at best, the same ineffective and dangerous care and treatment protocols which had previously, repeatedly and unsuccessfully been applied, as a result of following standard guidance in relation to the acute form of the condition; and

(b) at worst, no care at all, which is the current short term reality for all 900+ Patients, given the categorical failure of Dr Jennings and Whittington Health to arrange appropriate alternative care for Patients (as set out below).

Failings of Dr Jennings and Whittington Health to arrange appropriate alternative care for Patients

Given the foreseeability of the Closure of the LUTS Clinic (as addressed in Section 3 (*Clarification as to the closure of the LUTS Clinic*) above), Dr Jennings and Whittington Health were (and still remain) under a duty of care to ensure appropriate alternative care arrangements are in place for Patients.

Set out below is a list of the alternative care arrangements that Patients were assured were in place, and a summary of the outcomes of those assurances to date.

Date / source	Promise	Outcomes as at the date of this submission
22 October 2015 Letter to Patients from Dr Jennings	"*We will be writing to you again within the next two weeks to invite you to attend an appointment at an alternative clinic to review your care. In the meantime, if you are unwell, or if you continue to have symptoms, please make an appointment with your GP*"	• No Patient has received any such 'invite'. • No Patient has attended any appointment at an alternative clinic under this promise. • Patients' GPs have been unable to provide satisfactory assistance, given their lack of specialist knowledge. • The LUTS patient Helpline, while run by sympathetic staff, is not equipped to provide any medical advice or guidance, rather functions as a call-logging facility. • Many Patients are not receiving information from Dr Jennings or Whittington Health, but rather only discover information through the Facebook support page set up by Patients. • Many Patients describe an inability to get through to the LUTS patient Helpline; with many trying for days and/or leaving messages that have not been returned. • Only a very small handful of Patients have received a personal communication from a 'clinical expert' (these have only occurred in the last few days). Our understanding is that the two (and possibly the only) such experts involved have been microbiologists Dr Michael Kelsey and Julie Andrews. Patients describe the advice and support received as wholly unsatisfactory. • Especially vulnerable Patients and Patients with serious health exacerbations have not been adequately communicated to or cared for. • Some Patients have already been admitted to A&E.
2 November 2015 Letter to Patients from Dr Jennings (sent by PALS)	"*We have set up a multi-disciplinary team of clinical experts who will work together to address individual clinical queries that we have received. We will respond as quickly as possible by either: a telephone call, an email or a letter. This team includes senior clinicians specialising in Urology, Microbiology, Gynaecology, Pharmacy, and drug side effects and complications. If you have contacted us with such a query please be assured that a member of that team will be in touch. Should you have any queries meanwhile, please contact the LUTS patient helpline on 0207 288 5150. This will be active Monday to Friday from Monday 2nd November 2015 between the hours of 10.00am - 2.00pm.* *As one of those patients, you will be offered an outpatient clinic appointment. This is currently being set up and will be run by the clinical specialists described above*."	

Attached as Appendix H is a sample of Patient accounts as to their first hand experience of the inadequacy of the replacement arrangements that were put in place by Dr Jennings and Whittington Health. It is the view of Patients that Dr Jennings and Whittington Health have utterly failed in this duty of care to provide appropriate alternative care arrangements for Patients.

Dr Jennings himself stated in the 12 November Trust Meeting:

> "*What we tried to do was to put into place a group of clinicians that would be able to respond to patients concerns one by one. We haven't done this well. We haven't had the clinical capacity to respond as we would like – particularly because of the complex nature of the condition and the risks themselves*."

Such inadequacy amounts to a breach of certain NHS rights and pledges as set out in **Appendix D**.

One further point to highlight, Dr Jennings, at any time once realising the impact, could have reversed the Clinical Restriction to Standard Guidelines, which would have at least temporarily resulted in the re-opening of the LUTS Clinic. This would ensure continued Patient care while alternative arrangements were set up, pending the appropriate assessment and review of the Patient Incident and an appropriate, proportionate response to it. Each day, Dr Jennings elects not to do this.

8. Impact on Patients

In our cover letter to this Deputation we have described just some of the symptoms and effects to Patients suffering from Chronic Intracellular Bacterial UTI. It is difficult to succinctly describe the impact that the Closure of the LUTS Clinic has had on Patients, so we have **attached as Appendix I**, a sample of Patient impact statements. We hope that you take the opportunity to read these so that you may fully understand the profoundly severe impact that the Closure of the LUTS Clinic has had on us all.

If the Clinical Restriction to Standard Guidelines is allowed to stand, Patients will not be able to be treated in accordance with PML's Treatment Protocol. We will therefore be condemned to receive the same ineffective treatment provided under standard guidelines (or no treatment at all) which can, and will, have far reaching and severe consequences for all Patients.

9. Breaches of the NHS Constitution and Human Rights Act

A list of the patient rights and NHS pledges contained in section 3a of the NHS Constitution and the manner in which they have been breached as a result of the Clinical Restriction to Standard Practice, is **attached** as **Appendix D**. This list also importantly details breaches of Patients' human rights under the Human Rights Act 1998 and the indirect gender discrimination against the overwhelming majority of Patients. As a result of these breaches, the decision to impose the Clinical Restriction to Standard Guidelines can be considered unlawful.

10. Information about Chronic Intracellular Bacterial UTI

To assist you with your understanding of our condition, and in case of interest, we have **attached** as:

(a) **Appendix J**: a research paper that summarises all of PML's publications; and

(b) **Appendix K:** an addendum to PML's Treatment Protocol, dated April 2014, which addresses the concerns inevitably raised when long established assumptions to standard guidelines are challenged. An important extract from this as follows:

> "*We do realise that this approach is unusual and contrary to what has been taught. Questioning standard guidelines and tests is unwelcome. We have attracted plenty of criticism and scepticism but we can answer with the evidence from our science. This evidence has been growing steadily for some years. We are not treating our patients speculatively, but by drawing on an empirical evidence set that has been collected during the last 20 years.*
> *Well aware that we should attract criticism, we ensured, through governance and external review, that our science was meticulously careful with all studies repeated a minimum of thrice. Other centres, particularly in the USA and Australia, are now reproducing our results. The antibiotic policies were developed using empirical methods of evolutionary epistemology, developed by John Dewey, Karl Popper, Konrad Lorenz, Donald Campbell, and Stephen Toulmin. We are confident that the science has been rigorous, conscientious and duplicated many times.*
> *We were most conscious of safety during the development of these regimes and remain so*."

11. Patient goals

As a short term goal, the Patients wish for the Clinical Restriction to Standard Guidelines to be lifted immediately, so that Professor Malone-Lee is able to re-open his clinic and treat his 900+ Patients in accordance with PML's Treatment Protocol.

The long-term goal of the Patients is the recognition by the wider medical community of the existence of Chronic Intracellular Bacterial UTI as a condition that is separate and distinct from acute or recurrent cystitis, urinary tract infection or UTI and the acknowledgement and support of PML's research and PML's Treatment Protocol.

Mr Pleydell (the Chief Executive of Whittington Health) stated at the 12 November Trust Meeting that:

> "*We are meeting urgently with all the clinicians involved that are trying to help and we will be meeting with Professor Malone-Lee again to see if we can find a way forward that is appropriate for the Professor and in terms of our views on patient safety.*
> *We cannot prejudge the outcome of our discussions, but given the strength of feeling, and the current situation facing our patients, we are committed to finding a way forward with the Professor to look after you appropriately.*

We must agree a way forward that protects you, the Professor and the balances of risks we are concerned about...

We are very keen that [Professor Malone-Lee's] *research should continue and we would like to collaborate with other centres so that we can develop a strong evidence base that is badly needed.* [The Patients'] *concerns have made it very clear to us that we must put a plan in place to the future. We must involve colleagues from the CCG to secure the future of the service. I was in discussion with senior colleagues at the CCG today to make them aware of this meeting. I will reflect back to them urgently your passion and concern about the future of the service.*"

We hope that as part of your recommendation to Whittington Health and the Secretary of State for Health that you will support both the above short term and long-term goals and recommend that Mr Pleydell remains true to his words.

Once again, the Patients of the LUTS Clinic thank you for your time and consideration of this Deputation.

DEPUTATION STATEMENT

on behalf of the Patients of the LUTS Clinic, Whittington Health

APPENDIX A

Lower Urinary Tract Service (LUTS) Patient Meeting 12.11.15

Time 6.00pm – 8.00pm

Venue: Conference Hall, London Resource Centre, 365 Holloway Road, London N7 6PA

Please note: The following is a summary of the questions that were asked and the answers that were given. Where possible, questions have been grouped according to themes.

Scope of meeting

Simon Pleydell, Chief Executive Officer at Whittington Health welcomed patients and families and introduced the two additional members of the panel who would be answering questions – Dr Richard Jennings, Medical Director and Consultant Physician and Carol Gillen, Acting Chief Operating Officer responsible for the day to day running of the Trust.

The meeting was convened at the request of patients who felt that they had not had sufficient opportunity to air their concerns at the recent Trust Board meeting (4 November 2015) and was put together as quickly as possible in recognition of the urgent concerns many patients had.

The meeting will be focused on the panel listening to patients' concerns, giving those affected the chance to ask questions about the suspension of the clinic, future plans and some of the patient safety risks that motivated the suspension.

In advance of the meeting a number of patients had requested that the press not attend the meeting. Any members of the media were asked to leave the room to ensure patient confidentiality. Patients were reminded that they were entitled to speak to the press about their experiences outside of this meeting.

One patient identified themselves as a journalist and was asked not use the meeting as a source of reporting.

To ensure an accurate reflection of the questions and comments made the session was recorded. These notes are a summary of the questions and answers given at the meeting.

Opening remarks

Simon Pleydell: Despite the very real safety concerns our clinicians have, everyone at Whittington Health has been struck by the very profound concerns everyone at the meeting has about the future of the service. Because of the complexity of everybody's individual needs, the mechanisms that were in place meant we haven't been able to keep up in replying to people effectively.

Yesterday I asked our leading clinicians if we were responding properly and their answer was no. I want to be honest about that. We have tried our best but the complexity has been difficult and we will try and give you the answers that you need today.

The full board is not present today, this is due to the fact it was better to hold this meeting as a matter of urgency rather than wait for all members to be available.

Q: Why isn't the Professor present at the meeting?

Simon Pleydell: This is a chance for the Trust to meet with you to hear your concerns. We are meeting with the Professor tomorrow in light of our discussion to try and agree a way forward.

We know that there is a Facebook group that represents a number of patients who would like to make a statement. We would like to invite them to speak first.

Statement from Facebook Support Group

Thank you for organising the meeting and allowing us to speak today.

I'm a member of a patient support group of over 200 people suffering with chronic urinary tract infection – this is made up of sufferers from across the UK and all around the world.

I'm speaking on behalf of many of them today.

I'd like to understand more about the judgement call that contributed to the decision so I'd like to start by asking Dr Jennings to outline some of the typical symptoms of people suffering with LUTS?

Richard Jennings: I've received personally 200 – 300 emails and letters from patients and carers from the LUTS clinic. All of these letters describe the symptoms of LUTS to me. Some people have emailed me four or five times and haven't yet received a response and I'd like to start by apologising to you all. If I was patient and I was writing to the Medical Director, then what I would like is a personal reply to my personal questions.

Let me say there is a wide range of symptoms that people have described to me including pain, urinary frequency, not being able to get out of bed, feelings of despair at not being able to access the type of treatment they feel can help them. Some people have described thoughts of self-harm which is of great concern to me. I am aware of a whole range of different symptoms. Not everyone is identical but these are the common themes I can pick out.

Q: How many of the Professor's current patient list did you review before taking the decision to suspend the clinic?

Richard Jennings: When I made the evaluation about what had happened I did not go through a review of all the histories in the clinic and it would not have been practical to do so. That was not the question in front of me. The question in front of me was what to do about a patient who had suffered severe harm as a result of being given antibiotics at a dose and duration than is much longer than is usual and in a way that mirrored severe harm suffered by another patient six years earlier by another patient with the same antibiotic in the same way.

Q: Are you familiar with the Trust's risk management strategy? Did you make such a risk assessment when deciding whether or not treatment regimens are allowed to continue?

A Risk assessment for the individual patient who suffered harm will be properly made in an individual investigation which is not conducted by me, and that's the serious incident investigation. For any individual patient about whom an incident investigation is being conducted, a risk assessment will be made as to how likely that event would be to occur again if nothing more was done. A second risk assessment is also done to establish whether how likely it is to occur again if the risk mitigation measures recommended by the investigation are put in place.

Q: Did you do a risk assessment for the consequences to patients for withdrawing the Professor's treatment regimens?

Richard Jennings: I certainly assessed the risk of imposing a practice restriction on antimicrobial prescribing in the clinic. I would emphasise – and I know that Professor James Malone-Lee has explained this to his patients – is that what I said to Professor Malone-Lee is that I wanted him to prescribe within guidelines which had been created within the Trust for the purpose of ensuring that prescribing within the clinic was safe. Professor Malone-Lee felt that he couldn't continue working in the clinic under that practice restriction.

Q: Are you familiar with section 3A of the NHS Constitution the enshrines the patient right that should a local decision be made to deny treatment or drugs that your doctor feels are appropriate for you, for that decision to be rational and follow proper consideration of all the evidence? Would you say that having reviewed no patient histories and having failed to carry out any risk assessment for the consequences of withdrawing treatment you were able to make a rational decision, having properly considered all of the evidence?

Richard Jennings: What we have not anticipated is all the different aspects of complexity that have occurred since the practice restriction on 21 October. The distress that the restriction has caused, the pain that is has caused people and the difficulties we have had in producing a responsive alternative for you were not fully foreseen.

My actions were not breach of the NHS Constitution or a failure to take the correct approach to risk. One of the heaviest responsibilities on me as Executive Medical Director at Whittington Health is to make sure that our treatments are safe. This decision was not made by me alone. I spoke with the Medical Director for NHS England covering the London region, Dr Andy Mitchell, who fully supports the Trust in our decision.

A paper was submitted by the support group looking at the risk of withdrawing treatment against the benefits.

Richard Jennings thanked the group for their submission.

Q: Professor James Malone-Lee took patients on when conventional medicine wasn't able to help. Our quality of life was unbearable. The way the suspension has been handled has been really bad. The PALS helpline manned by non-clinical staff couldn't help me. Was the decision you made that caused the Professor to walk out a political one? I was told you would contact me and you didn't.

Richard Jennings: I want to start by saying I am sorry you were told I would contact you and I didn't. I am sorry that patients haven't had the timely support that they are entitled to.

Q: Now that the clinic is suspended what is currently in place for patients? Where is the Trust's duty of care?

Richard Jennings: We do have a duty of care. What we tried to do was to put into place a group of clinicians that would be able to respond to patients concerns one by one. We haven't done this well. We haven't had the clinical capacity to respond as we would like – particularly because of the complex nature of the condition and the risks themselves. When a patient safety event occurs you have to respond immediately to address that risk. We now need to look more closely at the physical and psychological risks to patients.

Q: We were told we would get an appointment within two weeks and haven't heard anything. We haven't even had a telephone call. Why is there no plan in place? What will happen in the short-term?

Richard Jennings: We will take questions about specific situations to our medical team and respond in order of priority. To date we have not been able to do this effectively due of the number of patients involved – and we are committed to doing something about this.

Q: Why didn't you put something into place before suspending the service?

Richard Jennings: The intervention that was made in the LUTS clinic was to protect patient safety immediately. The intervention was focussed on prescribing practices

and not an intervention about closing the clinic. Professor James Malone-Lee – a person the Trust and I have huge respect for – made the decision that he was not able to continue the clinic. Closing the clinic was not a restriction imposed on him by the Trust. This meant we weren't able to put in place the systems we would have wanted in order to fully support patients.

Q: How can patients who need Botox treatment arrange this?

Richard Jennings: Patient safety concerns are around antibiotics only and we will ensure that all patients who require Botox are able to access it.

Q: Is this a political issue?

Simon Pleydell: This is not a political issue. The actions that have been taken are as a result of a genuine concern for patient safety.

We are meeting urgently with all the clinicians involved that are trying to help and we will be meeting with Professor Malone-Lee again to see if we can find a way forward that is appropriate for the Professor and in terms of our views on patient safety.

We cannot prejudge the outcome of our discussions, but given the strength of feeling, and the current situation facing our patients, we are committed to finding a way forward with the Professor to look after you appropriately.

We must agree a way forward that protects you, the Professor and the balances of risks we are concerned about.

Q: My GP was told in July that people who were having Botox were not to be referred back to Professor Malone-Lee for their follow up. Has the closure of the clinic been on the cards for a long time? If so, why didn't you put plans in place then? Is the service still being commissioned? Has the clinic been closed to reduce the cost of prescribing antibiotics to the Trust?

Simon Pleydell: It is absolutely not true that the clinic has been suspended due to the costs of prescribing antibiotics. We are focussed on caring, quality and safety. We know that in this situation we haven't delivered but we are working with Professor James Malone-Lee to reach a solution.

Haringey and Islington CCGs have made it clear that they want to decommission the clinic – that was not pursued this year. I am still in discussion with the CCGs about the long-term future of the clinic. Only about 40 per cent of Professor Malone-Lee's patients attend from the locality and 60 per cent come from outside London. Therefore it is a very difficult decision for a part of the clinic to be decommissioned.

We do also need to discuss with Professor Malone-Lee, some longer terms plans for the future of the clinic as he is coming towards the end of his career to make sure we have clear plans for every individual to make sure we know how we are going to care

for everybody in the longer term. What is clear that if we do not do this we will not be able to support you properly.

I have discussed the current situation with the two accountable officers at the CCGs and I am in debate with them about long-term plans. The CCGs have views on the orthodoxy of prescribing in the way that Professor Malone-Lee does and this also needs to be discussed.

Q: If the CCG intends to decommission the service why haven't they consulted the patients?

Simon Pleydell: The Joint Overview and Scrutiny Committees have a duty to look at consultations and what the CCG request. We are commissioned by the CCG to provide this service. We can challenge them on their decision to decommission – although the suspension of the service is concerned with safety and not decommissioning.

Q: What kind of organ problems and side effects caused the suspension of the clinic? When can I discuss my situation with a medical professional?

Richard Jennings: Each patient needs an individual discussion to understand that particular set of risks they may be facing. This has not happened at the speed it should have done. The clinic was suspended without notice for us, meaning we were unable to give our patients any notice.

Q: Which antibiotic has led to the patient safety concerns you've raised? Why haven't patients been told?

Richard Jennings: It is right for us to answer this. The antibiotic concerned is nitrofurantoin. The case that caused us concern was a case of someone who had experienced organ damage as a result of taking nitrofurantoin being given in a way that doesn't fit with current guidelines. The organ damage that occurred is recognised as a side effect of taking this drug – one of the ways to limit the likelihood of this side effect occurring is to limit the length of time it is given to patients. In the case of the patient affected it was given to the patient for longer than recommended – we are currently looking into the circumstances surrounding this as a serious investigation within the Trust.

When talking about these cases of harm, we also have a duty of care to the patients affected to protect their confidentiality and we are not able to go into further detail.

We know that nitrofurantoin is not the only antibiotic that has risks associated with it and we hope that we can agree a prescribing regime covering all antibiotics with Professor Malone-Lee.

Q: Should patients continue to take the drug concerned?

Simon Pleydell: This is something that we need to discuss directly with Professor Malone-Lee as a matter of urgency and will advise patients as soon as we are able.

Q: How do you justify putting Professor Malone-Lee in such a difficult position through the practice restriction?

Richard Jennings: This exactly why we are meeting with Professor Malone-Lee to try and resolve this.

Q: Will NICE guidelines be imposed on Professor Malone-Lee?

Richard Jennings: We want to make sure the care you get is safe. We will be as flexible as we can to make sure we can deliver that, whilst still considering the complex risks facing patients.

Q: NICE guidelines are not compulsory. Can prescribing take into account patient consent?

Richard Jennings: I am sure we can look at existing recommendations and balance the situation to deliver a safe service but this will need to be considered very carefully.

Q: What guidelines are being considered – is it for acute UTIs?

Richard Jennings: The guidelines we are considering our guidelines that were drawn up within our own Trust that were developed with our antimicrobial steering group and the Drugs and Therapies Committee. The guidelines highlight what the effects and the potential side effects of antibiotics are, as well as the recognised and recommended durations are.

Not everybody has a condition that can be neatly managed within a guideline. These guidelines are intended as a guide and we hope to review this with Professor Malone-Lee.

Q: There have only been two incidents of harm in 900 patients. Why suspend the clinic based on such a small number of affected patients?

Richard Jennings: We understand that side effects from antibiotics can happen in healthcare. But if the same severe thing happens twice, we have to ask ourselves if the service is safe. We have a duty to make sure that we put the correct safety net in place to make sure this doesn't happen to other patients in the future.

Q: Why are patients not being given the choice to give their consent to the treatment affected?

Richard Jennings: It is true that in some areas of healthcare, such as major surgery, some patients will agree to consent to treatments that may put their lives at risk, but

this principle that patients should be fully informed of risks and benefits and then give informed consent to treatments doesn't absolve us of our duty of care to be safe.

Q: Will the Trust be withdrawing other treatments that involve the use of long term antibiotics? Or other treatments that have risks associated with them, such as chemotherapy?

Richard Jennings: Everything that we do in healthcare can involve risk and this is a fair question to ask. Risk is complex and we have to make individual judgements on each treatment.

Q: Many clinicians prescribe off-licence. Why only Professor Malone-Lee has been highlighted?

Richard Jennings: We must learn from patient safety incidents in order to be safe. What is particular about this case is that we have had the same safety event, the same severe harm, in the same way, with the same drug – twice. We must make sure that we are taking the right steps to learn when things happen more than once.

Q: Do you really care about your patients?

Richard Jennings: We are sorry. We are absolutely aware that all of our patients in the LUTS clinic have had an awful experience and we are profoundly sorry for all the distress the suspension has caused. We haven't been able to manage the situation as well as we would have liked.

Q: What will be the long-term treatment plans for patients? Short term antibiotics are not effective.

Simon Pleydell: The practice restriction was not made with the CCG, this is something our medical team and other senior clinicians in the NHS decided to take regarding patient safety. It maybe that the balance of the restriction needs to be reviewed and we are meeting urgently with Professor Malone-Lee to discuss this.

Q: How likely is it that the clinic will resume in light of patient feedback?

Simon Pleydell: If our discussion go well with Professor Malone-Lee I am hopeful that we can get to a place where we can reinstate the clinic. This will be dependent upon us reaching an agreement with the Professor that means we are able to satisfy both the safety and patient needs.

We have a duty of care to all our patients and we are committed to reaching an agreement with Professor Malone-Lee.

We cannot predict the outcome of these discussions at this stage.

Q: What is the long term plan given that Professor Malone-Lee is due to retire and reluctance of the CCG to recommission? Why are other doctors not equipped to be able to continue the work of Professor Malone-Lee?

Simon Pleydell: This is a point very well made and the person to help us with this is Professor Malone-Lee himself. We are very keen that his research should continue and we would like to collaborate with other centres so that we can develop a strong evidence base that is badly needed.

Your concerns have made it very clear to us that must put a plan in place to the future. We must involve colleagues from the CCG to secure the future of the service. I was in discussion with senior colleagues at the CCG today to make them aware of this meeting. I will reflect back to them urgently your passion and concern about the future of the service.

The patient group submitted a 64 page review of existing evidence to the Trust for consideration.

Q: Can the Chair confirm that this meeting is recording informally or otherwise the number affected patients, carers and relatives?

It was recorded that 120 patients, 40 partners and 30 carers attended the meeting.

DEPUTATION STATEMENT

on behalf of the Patients of the LUTS Clinic, Whittington Health

APPENDIX B

Protocol for management of patients with chronic lower urinary tract symptoms with clinical evidence of urinary tract infection – Whittington Lower Urinary Tract Symptoms Clinic

Update Nov 2014
James Malone-Lee MD FRCP

The evidence for the practices described in this protocol have been reviewed briefly in a separate accompanying paper.

Problems

The patients referred to this centre have failed treatments in primary and secondary care so that by definition all standard protocols and guidelines have been unsuccessful. Nowadays a steady stream from tertiary care centres augments this situation.

Inevitably we must treat patients differently to standard guidelines. Any specialist academic centre should act similarly. Our regimes rely significantly on protracted courses of high doses of antibiotics, often in combination. There is solid evidence for these approaches to care, albeit in specialist scientific literature. This centre supports a busy discovery clinical science programme which is gleaning the evidence and a rich source of safety data. There is a clinical governance structure in place.

We are aware that the treatment methods are unconventional and inimical to a number of quality targets. However, techniques have their origins in discoveries of serious flaws in accepted urinalysis, quantitative urinary microbiological culture and the assumptions that are promoted in best practice recommendations for treating urinary tract infection. Several research groups in the UK and USA have identified these errors but the implications are substantial so they have been greeted with scepticism. Cognisant of this climate, the research that informs this practice has been careful, eclectic, and repeated as a minimum in triplicate.

A crux point is that absence of evidence of disease it not the same as evidence of absence.

Typical patient

This protocol covers the management of patients with lower urinary tract symptoms likely to include recurrent urinary infections, chronic bladder pain, interstitial cystitis and chronic cystitis. Their symptoms have been present for an average of five years. The mean age of the patients is 50 (95% CI 48 to 51), 80% female 20% male. All will describe a history of multiple tests and consultations in secondary and tertiary care. The story of symptoms despite numerous normal urinalyses is common and most patients believe that doctors think there is nothing wrong with them. The typical investigations that have been used include blood tests, renal tract and pelvic ultrasound, CT scans, MRI scans, and urodynamics. Most patients will have undergone cystoscopy, with or without urethral dilation or cystodistension. Bladder biopsies will have revealed various manifestations of chronic cystitis. It is common to

report multiple cystoscopies. Other than biopsy pathology, these investigations will usually have proved negative. A variety of bladder infusion treatments may have been attempted without benefit.

Outcomes

Using symptoms scores and analyses of urinary white blood cell excretion and urothelial cell shedding we have been able to measure the outcomes to the treatment regimes covered in this paper. The evidence gleaned implies that the treatments are successful in resolving these symptoms.

Abbreviations
Urinary tract infection (UTI)
Lower Urinary Tract Symptoms (LUTS)
White blood cells (wbc)
Urinary epithelial cells (epc)
Clean catch, interrupted, midstream urine sample after proper perineal preparation (MSU)
Extended spectrum beta-lactamase – (ESBL)

Communication

These notes are commensurate with the scripts that we use to explain our management methods which are used to communicate with the GPs and the patients. Both parties receive identical information.

Tools to assist diagnosis

Symptoms

Voiding symptoms
Pain symptoms
Incontinence
Urinary frequency
Urgency symptoms

Stress incontinence symptoms

History of recurrence and the story of management

Signs

Suprapubic tenderness
Loin tenderness
Urethra tenderness
Prostate tenderness

Testing

Urinary pyuria >0 wbc μl^{-1} (zero wbc μl^{-1}) on microscopy of an immediately fresh unspun properly collected MSU sample

Urinary epithelial cell count >0 epc μl^{-1} (zero epc μl^{-1}) on microscopy of an immediately fresh unspun properly collected MSU sample

MSU to laboratory for routine culture

Urinary spun sediment culture in selected cases

Lung function tests (If respiratory symptoms indicate for Nitrofurantoin)
Liver function tests (Antibiotic exposure based on clinical judgement)
U&E & Creatinine (On clinical judgement and for gentamicin preparation)
FBC (On clinical judgement)
Inflammatory markers (On clinical judgement) – These may be inappropriately reassuring

Monitoring disease progression and resolution

We generate plots of symptoms, pyuria and epithelial cells on a time axis. These are expected to show a damped oscillation featuring a series of peaks falling slowly towards full resolution; this is a damped oscillation (Figure 1). The last curves to settle are likely to be the symptoms plots. The symptoms must dictate the treatment decisions because they are the most sensitive indicators of disease; nevertheless the wbc and epc counts are validated markers of disease activity. These different properties mean that antibiotic treatment will continue to be administered during periods when the urinalysis is negative because the symptoms dictate this circumstance. A number of patients will show plots that fall to the baseline without oscillations on the way; a critically damped oscillation (Figure 2). Patients who struggle to respond will show more disordered graphs; undamped oscillations (Figure 3) but these should not dismay, they can be brought under control.

Figure 1
A damped oscillation

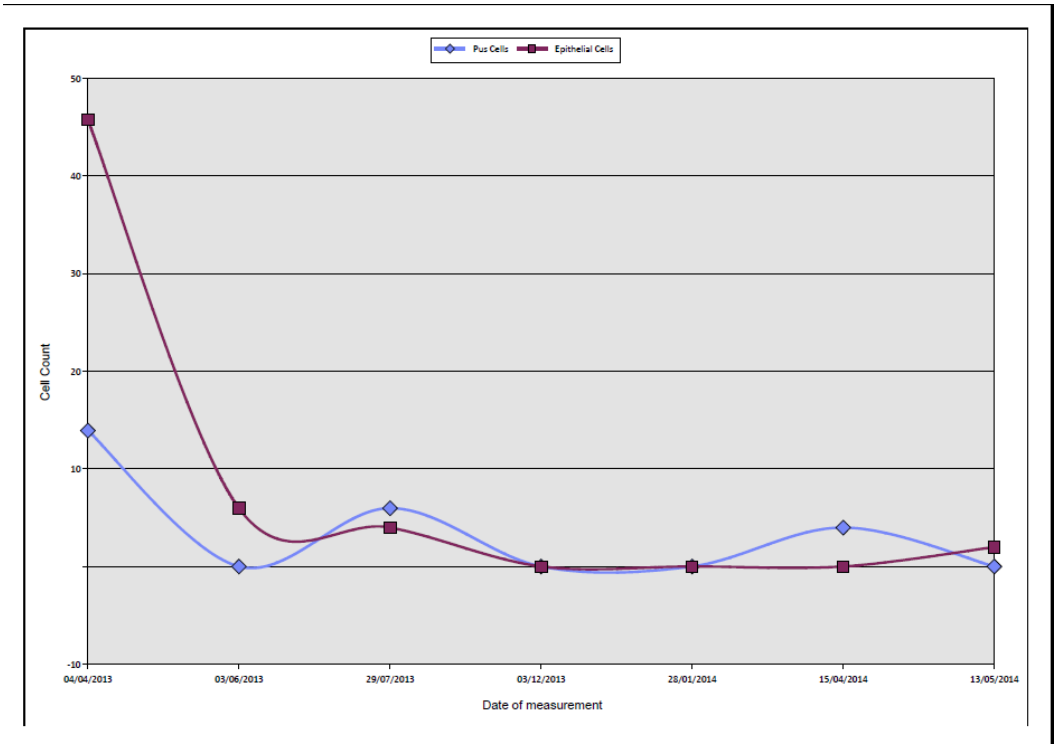


Figure 2
A critically damped oscillation

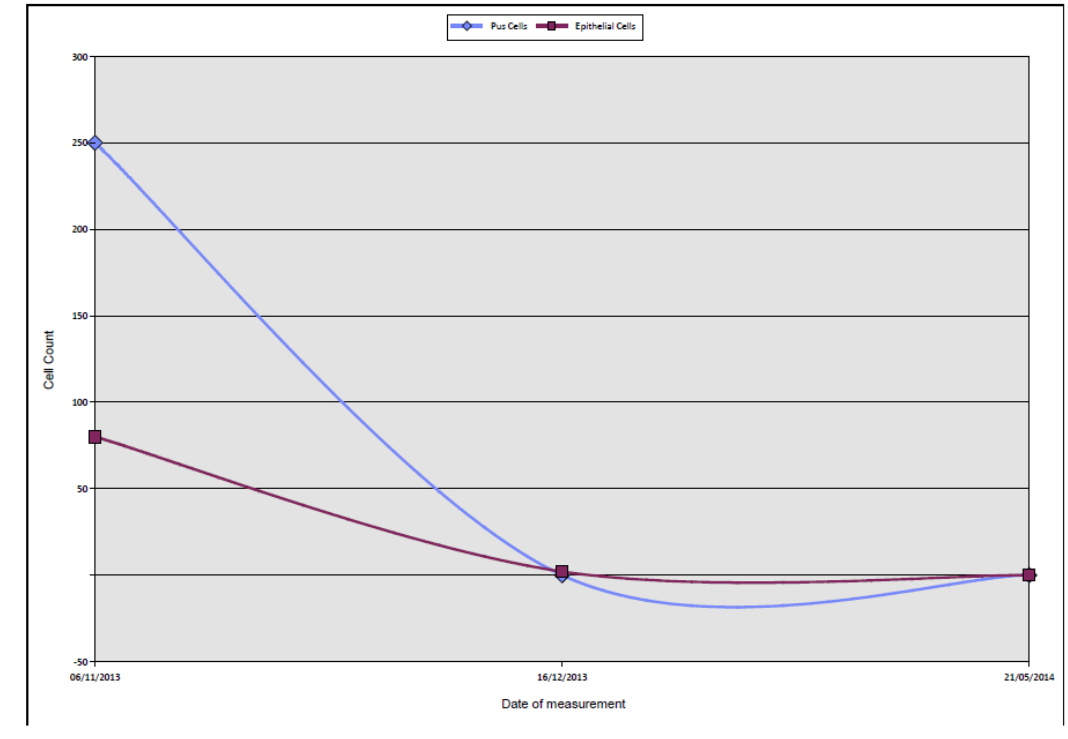
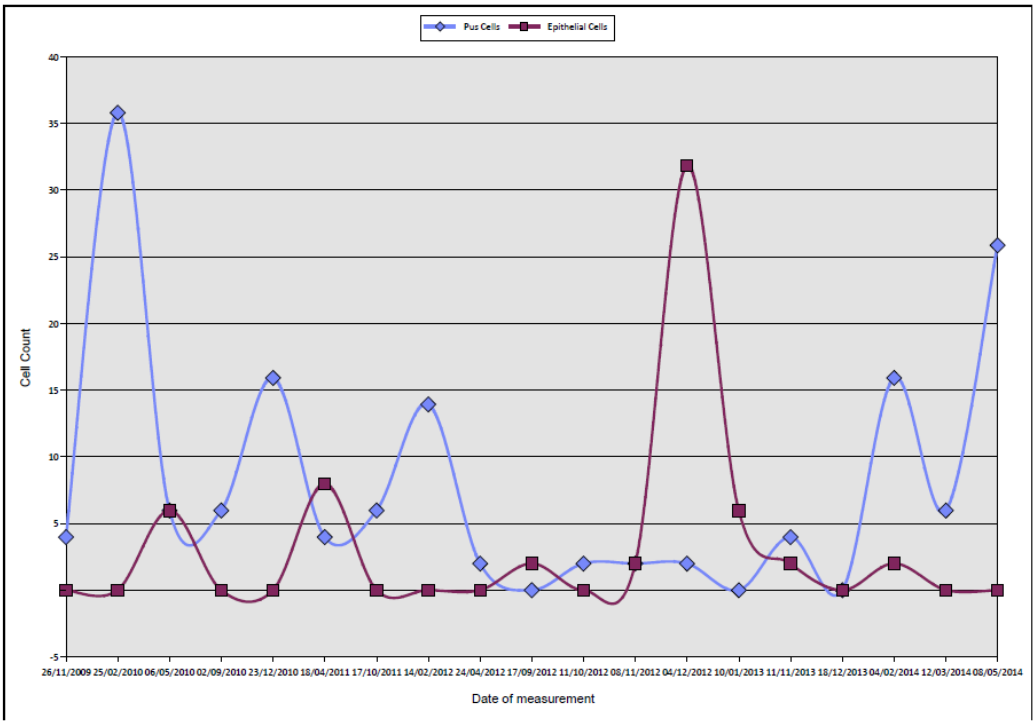


Figure 3
Undamped oscillation



Problems to be confronted

These infections are commonly long-term and have been exposed to partial treatment strategies. The infections are more likely to be polymicrobial. There are problems with E.coli forming very tight biofilms on the urothelial cell surfaces, and enterococci colonise the interior of the urothelial cells. At this time we do not know the behaviour of other microbes in relation to the cells although the infections associated with them imply a close urothelial cell association. We are suspicious of the influence of non-culturable, obligate intracellular, fastidious microbes.

The cell-associated properties of these microbes make them resistant to antibiotic attack. Penetration of the cells and biofilms is difficult and demanding of high doses of antibiotic to achieve adequate urine level. There is less of a problem with resistance than might be assumed.

Many patients believe that they have not been listened to and their problems dismissed. They may mistrust clinical staff, feel angry and they can be unusually assertive. All this is understandable and in many cases it is appropriate. The clinicians must do their best to be kind, patient and sympathetic, always ensuring that the story and symptoms are acknowledged and recorded.

To control and clear these infections we have to use long-term antibiotic treatment. This is not welcome in our current culture and effort must go into reassurance and explanation of the reasons and motivation for such treatment regimes. Every

prescription must be associated with a reasoned explanation of the purpose and expectations

Antibiotic options

First line

(1) Nitrofurantoin Macrocrystals CR 100 mg bid to 100 mg qid – If the CR formulation is not available you must spread the ordinary Nitrofurantoin Macrocrystals over a four dose schedule. Be aware of chest, neuropathic and live side effects.

(2) Trimethoprim 200 mg bid to 400 mg bid – Be aware of a 40% resistance rate but it can be useful provided that you are on the look-out for a failed response

(3) Cephalexin 1 gm bid to 1 gm qid (Cephalexin is a first generation cephalosporin and it has one of the lowest C.Diff rates of all antibiotics)

Second line

(1) Azithromycin 500 mg daily for three days and then thrice weekly (Particularly in the presence of urethral pain; male LUTS with urethral and prostate pain; symptoms associated with low level pyuria with or without elevated epithelial cell shedding) If response dips occur between doses then the prescription should rise to 500 mg daily. Be aware of concomitant medication that may influence elimination and the potential effects on the QT interval in the ECG.

(2) Doxycycline 100 mg bid (Particularly in the presence of urethral pain and males LUTS with urethral and prostate pain)

(3) Pivmecillinam 400 mg bid to 800 mg tid

(4) Amoxicillin 500 mg bid to tid

(5) Co-amoxyclav 500 mg bid to tid (We try to avoid this antibiotics because of the problems with side effects)

Methenamine Hippurate (Hiprex)

Methenamine is an important adjunct that turns the urine into an antiseptic. We aim to use it in most patients on long-term regimes and it is very helpful in achieving sparing of antibiotic use. We tend to introduce it after the first-line regime has been established

Response to candida infections identified by urinary yeasts

If you notice a raised pyuria with no exacerbation of the main symptoms set always be suspicious of candida infection. The yeasts are often seen on microscopy of the urine.

(1) Vaginal candida is best treated topically Clotrimazole vaginal pessary 1 thrice weekly– listen carefully and ascertain whether bladder symptoms are part of the clinical picture

(2) Fluconazole 100 mg daily for seven to 14 days

(3) Candida can be resistant so be ready to seek microbiological advice

Third line

Fosfomycin 3 gm thrice weekly (only when combined with another agent)

Fourth line

Ciprofloxacin 500 mg bid: We seek to avoid this if at all possible. It should also be noted that it frequently achieves an acute effect but cannot hold control in the long-term so it is really a short-term crisis medication.

Fifth Line

If patients claim penicillin sensitivity check this with skin tests.

Nowadays we are resorting to IV regimes on very rare occasions. We have got the rate down to 0.15% of patients. This approach may be used exceptionally but only in the light of a sediment culture with sensitivity analysis. We should always discuss this option with the microbiologists and we must have good sediment culture data to brief them.

Ertapenem 1 gm IV over 30 minutes daily for five days

If penicillin intolerant

Gentamicin 7 mg / kg once daily IV for five days.

In some very unusual circumstances when dealing with very long-term ingrained infections we may use longer courses of these preparations. The sediment culture may encourage us to use a different antibiotic agent

How to manage the regimes:

Make your initial antibiotic choice on the history of past tolerances and response.

In all cases we must use a full therapeutic dose. Note that some patients can notice a resurgence of symptoms after a single missed dose, this is not imagined. The use of the medication in full dose, usually twice daily is very important. We should do our utmost to stick to first generation antibiotics. Partial resistance is frequently overcome by higher doses or antibiotic combinations.

We should work with this list of antimicrobials altering the prescription in relation to response and tolerance. The majority of the time, routine cultures will be negative or reported as mixed growth of doubtful significance. Thus, antibiotic sensitivity data will not be readily available. Similarly dipstick analysis will often be misleadingly reassuring. The microscopic examination of immediately fresh unstained, unspun, urine in a haemocytometer is crucial to management. The pyuria and epithelial cell counts are relevant and like symptoms, should be plotted on a graph. Response must be judged on the evidence of the direction of change of the symptoms and urinalysis graphs. If there is a downward trend in these graphs then you should be reassured that the treatment is appropriate and stick with it despite the fluctuations.

An initial treatment may result in a symptoms, signs and urinalysis response without side effects. In such circumstances we should layer in Methenamine as an adjuvant to the antibiotic regime. Methenamine supports and effective regime and will assist eventual antibiotic cessation.

A good response may be disrupted by an acute flare. In such circumstances it is usually unwise to discontinue the previously effective regime because the flares commonly result from opportunistic microbes invading vacated space.

Ask patients about symptom manifestations between doses or following missed doses. These are not imagined and should motivate an increase in the frequency of administration.

Always ask about side-effects and work on the principle that they are unacceptable.

Intolerance is by far the commonest reason for altering the prescription and in some patients this can require a considerable amount of shuffling to find an effective, tolerated regime. This can lead to considerable multiplicity at the outset.

Efficacy failure is a valid reason for changing.

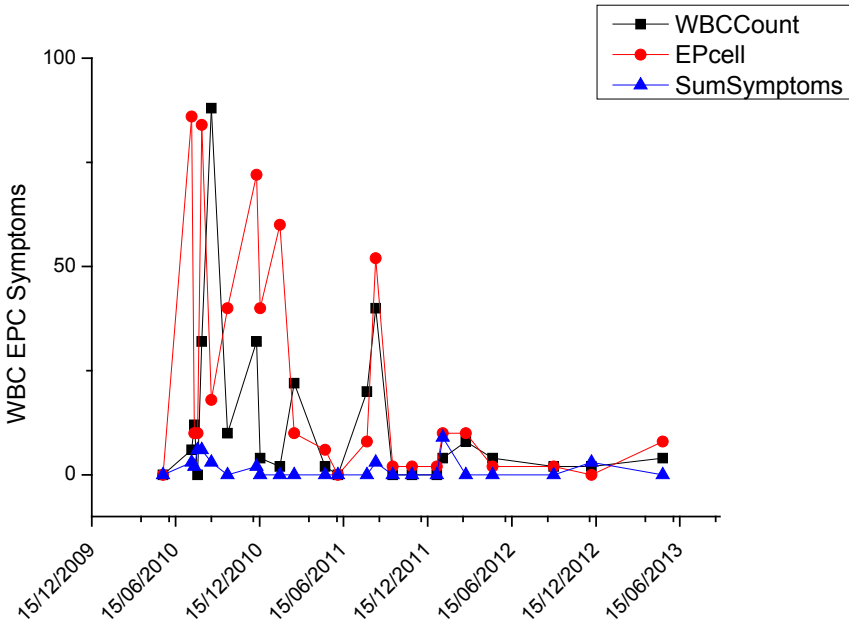
Because of the polymicrobial nature of these infections combination therapies may be required. These should be identified on evidence. Typically the patient has been responding to an antibiotic, which they are comfortable taking, when their course is disrupted by an acute flare. Initially this should be managed by increasing the dose of the current antibiotic if that is possible. Failing this, the regime should be changed but on many occasions the symptoms will deteriorate on the transfer to another antibiotic which implies that the original antibiotic was working on some part of the pathology and that there is another microbe to address as well. In such circumstances reintroduce the first antibiotic and work out the companion using the trial and error approach.

A mixed infection requiring combined therapy can sometimes be spotted because the symptoms making up the flare are of a different quality. Thus, listening carefully to what the patient says is extremely important.

To date the sediment culture is proving remarkably accurate in identifying the mixed pathology and so far the results have matched the clinical narrative very closely indeed. The sediment cultures are laborious, time consuming and costly so we have to use them sparingly.

The graph below (Figure 4) is a very typical plot obtained from a patient who proved a major struggle to bring under control. You should expect to see very similar plots but on shorter times scales.

Figure 4
A reluctant damped oscillation



Dealing with complications, failures and adverse events

We provide a very rapid access service for the patients via email. This is available to address failures of efficacy, adverse reactions, acute flares and prescriptions renewal. By and large we manage to respond within the 24-hours. By this we take full responsibility for the care of these regimes.

DEPUTATION STATEMENT

on behalf of the Patients of the LUTS Clinic, Whittington Health

APPENDIX C

Whittington Health NHS

Sent by Email

Strictly Private & Confidential
Addressee Only

Executive Offices
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21st October 2015

Dear James

Thank you again for coming to see me this morning. I am writing to confirm the formal restriction that I am placing on your clinical practice in my role as Medical Director. The restriction is that from now onwards your antimicrobial prescribing must adhere to the written guidance provided through the extraordinary meeting of the Joint Antimicrobial Steering Group (ASG) and Drug & Therapeutics Committee (D&TC) meeting on the 4th August 2015. While I believe you have this guidance already, I attach a copy here (appendix 1).

I must also ask you not to depart from this guidance when treating any of your private patients in any Whittington Premises.

I also need to ask you to kindly confirm that your private practice is only provided from Whittington premises. If you provide care to private patients from any other location, please would you let me know?

I believe Nick Harper is going to telephone you this afternoon to talk through arrangements for tomorrow.

Once again I would like to say that I understand that this situation is stressful for you and I would like to highlight again the opportunities for support that I outlined in my previous letter should you wish to use them: Occupational Health can be contacted via 020 7288 3351 or People @ Work can be contacted on 020 3286 1545.

With best wishes

Dr Richard Jennings
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Academic Health Science Partnership

DEPUTATION STATEMENT

on behalf of the Patients of the LUTS Clinic, Whittington Health

APPENDIX D

NHS CONSTITUTION Section 3a Breaches of NHS Patient Rights and NHS Pledges (includes Human Rights Act 1998 and Equality Act 2010 breaches)		
	NHS PATIENT RIGHTS	**Breach**
1.	**You have the right** to receive care and treatment that is appropriate to you, meets your needs and reflects your preferences.	Each of the 900+ Patients came to be referred to the LUTS Clinic because the management of their chronic cystitis in accordance with standard guidelines proved unsuccessful. The care that each Patient has been receiving at the LUTS Clinic was individually tailored and therefore appropriate for each individual, met the needs of each individual, reflected individual preference and, most importantly, was proving successful. The Clinical Restriction to Standard Guidelines has denied all Patients this important NHS right.
2.	**You have the right** not to be unlawfully discriminated against in the provision of NHS services including on grounds of gender, race, disability, age, sexual orientation, religion, belief, gender reassignment, pregnancy and maternity or marital or civil partnership status.	Given that 80% of the LUTS Clinic Patients are female and a similar percentage of future patients are statistically likely to be female, it is entirely arguable that the Clinical Restriction to Standard Guidelines has unlawfully discriminated against patients of the LUTS Clinic on the grounds of gender. Whittington Health has a duty of equality under section 14 of the Equality Act 2010. The Clinical Restriction to Standard Guidelines disproportionately affects women and therefore amounts to indirect discrimination, which is unlawful under section 19 of the Equality Act 2010. It is relevant to note that discrimination law is 'blind' and therefore the motive behind the discrimination is not relevant. The Patients are not aware of any objective justification for such discrimination, as and understand that an appropriate analysis of the equality implications of the Clinical Restriction to Standard Guidelines has not been undertaken by Dr Jennings or Whittington Health.
3.	**You have the right** to expect NHS bodies to monitor, and make efforts to improve continuously, the quality of healthcare they commission or provide. This includes improvements to the safety, effectiveness and experience of services.	Despite the breakthrough success of PML's Treatment Protocol for Chronic Cystitis, Dr Jennings and Whittington Health has failed to acknowledge the improvement in the quality of healthcare to LUTS Clinic patients. This has effectively breached all Patients' right of expectation in this regard.
4.	**You have the right** to be treated with dignity and respect, in accordance with your human rights.	The Clinical Restriction to Standard Guidelines have breached Patients' human rights under Article 3 (*freedom from torture and inhuman and degrading treatment*) of the Human Rights Act 1998, in that, as Patients can no longer be managed in accordance with the PML's Treatment Protocol for Chronic Cystitis, they are fated to suffering from the physical and mental pain, combined with feelings of fear,

		anguish, anxiety and depression, caused by chronic cystitis when being managed in accordance with standard guidelines for the acute condition. Further, the Clinical Restriction to Standard Guidelines have breached Patients' human rights under Article 8 (*right to respect for private and family life*) of the Human Rights Act 1998 by denying Patients treatment in accordance with PML's Treatment Protocol for Chronic Cystitis, as Article 8 applies to non-life-saving treatment where the denial of such would have a severe impact upon the quality of that individual's life or upon his private relationships.
5.	**You have the right** to be involved in planning and making decisions about your health and care with your care provider or providers, including your end of life care, and to be given information and support to enable you to do this. Where appropriate, this right includes your family and carers. This includes being given the chance to manage your own care and treatment, if appropriate AND **You have the right** to be involved, directly or through representatives, in the planning of healthcare services commissioned by NHS bodies, the development and consideration of proposals for changes in the way those services are provided, and in decisions to be made affecting the operation of those services.	There has been no attempt by Whittington Health or Dr Jennings to involve Patients in any aspect of the process which led to the Clinical Restriction to Standard Guidelines. Given the Clinical Restriction to Standard Guidelines directly and adversely affects the health of Patients, we consider this to be a breach of Patients' right to be involved in the planning and decisions about their health and care and the planning, proposals, changes and operation of the particular healthcare service provided by the LUTS Clinic.

	NHS PLEDGES	Breach
1.	(a) to provide you with the information and support you need to influence and scrutinise the planning and delivery of NHS services; (b) to work in partnership with you, your family, carers and representatives; and (c) to involve you in discussions about planning your care and to offer you a written record of what is agreed if you want one.	Given the profound lack of information received from Dr Jennings or Whittington Health, and the non-existent consultation with Patients, the Patients consider that Whittington Health has wholly failed in its against this NHS pledge to: (a) provide Patients with the information and support they need to influence and scrutinize the planning and delivery of the NHS service provided by the LUTS Clinic; (b) work in partnership with Patients; and (c) involve Patients in discussions about planning their care and offering a written record of what is agreed.
2.	to make decisions in a clear and transparent way, so that patients and the public can understand how services are planned and delivered.	Again, given the profound lack of information received from Dr Jennings or Whittington Health, the steps and decisions leading to the Clinical Restriction to Standard Guidelines have therefore been made in a way that wholly fails in this NHS pledge to be clear and transparent so that patients can understand how services are planned and delivered.
3.	to make the transition as smooth as possible when you are referred between services, and to put you, your family and carers at the centre of decisions that affect you or them.	The inadequacy of the replacement arrangements that were put in place for 900+ Patients have been robustly expressed by Patients in the collation **attached** as **Appendix H** to the Deputation. Accordingly, Patients consider that Whittington Health has wholly failed in its NHS pledge to make the transition as smooth as possible and to put Patients at the centre of the decision to issue the Clinical Restriction to Standard Guidelines, which has clearly affected each and every Patient.
4.	to identify and share best practice in quality of care and treatments.	Congruent with a breach of the Patient right identified in item 3 (*NHS Rights*) above, Whittington Health has wholly failed in its pledge to identify and share best practice in quality of care and treatments. It is clear that the Clinical Restriction to Standard Guidelines imposes an inappropriate and inadequate treatment approach for chronic cystitis sufferers, whereas the PML's Treatment Protocol for Chronic Cystitis has proven effective and successful.

DEPUTATION STATEMENT

on behalf of the Patients of the LUTS Clinic, Whittington Health

APPENDIX E

Whittington Health NHS

Joint Antimicrobial Steering Group (ASG) and Drug & Therapeutics Committee (D&TC) meeting

Extraordinary meeting

- Review of the "LUTS Clinic: Protocol for the management of patients with chronic lower urinary tract symptoms".

Held on Tuesday 4 August 2015 at 1pm

This joint meeting was held to review the 'Protocol for management of patients with chronic lower urinary tract symptoms with clinical evidence of urinary tract infection – Whittington Lower Urinary Tract Symptoms Clinic'.

Protocol review			
Protocol - First line		**Outcome of review**	**Consideration**
1	Nitrofurantoin Macrocrystals CR 100mg BD to 100mg QDS	This should NOT be given as **QDS**	Licensed dose = 100mg BD up to 7 days (Ref: BNF, SmPC). Nitrofurantoin Macrocrystals CR is formulated as a **prolonged release capsule** and should only be given twice a day.
		Treatment duration NOT stated.	Maximum licensed treatment duration = 7 days (BNF, SmPC). Prolonged therapy is associated with severe and sometimes irreversible peripheral neuropathy, and subacute or chronic pulmonary symptoms including interstitial pneumonitis and pulmonary fibrosis (may develop more insidiously)with the latter are not always reversible(Ref: Martindale).
Final recommendation re Nitrofurantoin Macrocrystals CR. **This product can be used as part of the LUTS clinic protocol but only at a dose of 100mg BD for a maximum duration of 7 days.**			
2	Trimethoprim 200mg BD to 400mg BD	This should NOT be given as **400mg** BD.	Licensed dose = 200mg BD. The FIRST dose may be doubled as a loading dose(Ref: SmPC). There are no published studies on the use of trimethoprim 400mg BD in UTI. High dose of trimethoprim is also reported to increase the risk of clinically important hyperkalaemia, which can be serious or life-threatening (Ref: Martindale).
		Treatment duration NOT stated.	Maximum licensed duration = 2 weeks for acute treatment (Ref: SmPC). High doses and prolonged courses have been shown to cause depression of haematopoiesis. This can manifest as megaloblastic anaemia, or as thrombocytopenia and leucopenia. Methaemoglobinaemia has also been seen (Ref: Martindale).

Final recommendation re Trimethoprim. **This product can be used as part of the LUTS clinic protocol but only at a dose of 200mg BD (apart from a loading first dose) for a maximum of 2 weeks.**			
3	Cefalexin 1g BD to 1g QDS (cephalexin is a first generation cephalosporin and it has one of the lowest C. diff rates of all antibiotics)	The dose range is loosely based on the license dosing.	Licensed dose= 250mg QDS or 500mg BD or TDS(may be increased to 1 – 1.5g TDS or QDS for severe infections or those cause by less susceptible organism) (Ref: BNF, SmPC).
		Treatment duration NOT stated.	Prolonged use of cefalexin may result in the overgrowth of non-susceptible organisms (Ref: SmPC).
Final recommendation re Cefalexin. This higher dosing regime of 1g BD to 1 g QDS can be used for selective patients for a maximum of 14 days.			

Protocol - Second line		Outcome of review	Consideration
1	Azithromycin 500mg OD for 3 days and then thrice weekly If response dips occur between doses then the prescription should be rise to 500mg OD.	**NOT recommended for UTI**.	Azithromycin in not used for the treatment of UTI. It has limited Gram negative activity and is not effective against *Escherichia coli*, Enterobacterspp, Klebsiella spp, and Proteus spp that cause UTIs (Ref: Kucer's). A small number of *in vitro* studies have explored the use ofazithromycin for *Pseudomonas aeruginosa* in experimental UTI model. It was suggested that azithromycin may inhibit biofilm formation and adhesion of *Pseudomonas aeruginosa* on urinary catheters, and reduce the swimming motility and the production of virulence factors of *Pseudomonas aeruginosa*(Xu 2015,Bala 2011,Fiaux 2013). Further studies are need in to support its use in humans for this indication. Azithromycin is use for genitourinary infections due to chlamydia, and is given as a single dose (Ref: SmPC).
Final recommendation re Azithromycin. This product cannot be used as part of the LUTS clinic protocol for use in patients with UTI.			
2	Doxycycline 100mg BD (particularly in the presence of urethral pain and males LUTS with urethral and prostate pain)	Licensed dose	Licensed dose for refractory/chronic UTI = 200mg daily(SmPC) Licensed dose for genitourinary infections = 100mg BD (SmPC)
		Treatment duration NOT stated.	For the treatment of acute infections, therapy should be continued for at least 24 to 48 hours after the symptoms and fever has subsided (Ref: SmPC). For STD, this should be given for 7 days (or 10 days for acute epididymo-orchitis) (Ref: Martindale).
Final recommendation re Doxycycline. This product can be used by the LUTS clinic protocol but with a maximum duration of 10 days for treatment purposes.			
3	Pivmecillinam 400mg BD to 800mg TDS	This should NOT be given as**800mg TDS**	Licensed dose for chronic / recurrent bacteriuria = 400mg TDS to QDS (Ref: BNF, SmPC, Martindale).
		Treatment duration NOT stated.	In published studies, treatment duration usually ranges from 5 to 15 days (Wise 1976,Brumfitt 1982,Jansaker 2014). In a study using pivmecillinam 200mg TDS for 3 months in female patients with chronic recurrent UTI who failed to respond to 10-day course of pivmecillinam and/or amoxicillin, 11% (3/27) of patients withdrawn from the treatment due to GI side effect and another 11% (3/27) described unusual sensation in the body and an affinity for salt which resolved after the discontinuation of treatment (Bresky 1982). Long-term use or frequently-repeated treatmentis associated with carnitine depletion. Symptoms of carnitine depletion include muscle aches, fatigue, and confusion (Ref: SmPC).

Final recommendation re Pivmecillinam. This product can form part of the LUTS clinic protocol at a maximum dosing of 400mg QDS for a maximum duration of 10 days.			
4	Amoxicillin 500mg BD to TDS	This should NOT be given as **BD**.	Licensed dose = 500mg to 1g TDS (Ref: BNF) No published study on BD dosing for UTI.
		Treatment duration NOT stated.	No published study on the long-term/prophylactic use for UTI. Prolonged use may occasionally result in overgrowth of non-susceptible organisms.
Final recommendation re Amoxicillin. This product can form part of the LUTS protocol but only at a dosage regime recommended by the BNF i.e. 500mg to 1g TDS. Maximum duration for treatment should be 14 days.			
5	Co-amoxiclav 500mg BD to TDS	This should NOT be given as **BD**.	Licensed dose = 375mg or 625mg TDS (Ref: BNF, SmPC) No published study on BD dosing for UTI.
		Treatment duration NOT stated.	No published study on the long-term/prophylactic use for UTI. The duration of treatmentshould not usually exceed 14 days (Ref: BNF).Risk of cholestatic jaundice and acute liver toxicity with prolonged treatment. In some cases, this may not become apparent until several weeks after treatment has ceased (Ref: BNF, SmPC).
Final recommendation re Co-amoxiclav. This product can form part of the LUTS protocol but only at the dosage regime recommended by the BNF for a maximum duration of 14 days.			
Methenamine Hippurate		**Outcome of review**	**Consideration**
Methenamine is an important adjunct that turns the urine into an antiseptic. We aim to use it in most patients on long-term regimes. We tend to introduce it after the first-line regimen has been established.		**Not approved by D&TC**	**Methenaminehippurate was rejected by the Drug & Therapeutic Committee (D&TC) in January 2012.** Extract from minutes of the meeting: *"Professor James Malone-Lee presented an application to add MethenamineHippurate/Hexamine Hippurate to the formulary. This is for managing of patients whom he is treating for chronic intracellular bacterial colonisation of the urothelium. These would be for patients with severe infections. There is no significant clinical data for this area however there is good observational evidence for this. However, this drug is needed as some patients are difficult to treat with other antibiotics.* ***Agreed: Not approved for the formulary. Committee members had suggested that this may be more appropriate if re-submitted for use on a short-term basis or used in a research context of a randomised clinical trial. Prof JML to be requested not to refer prescriptions for Hiprex® to GPs."***
Response to candida infections identified by urinary yeasts:		**Outcome of review**	**Consideration**
1	Clotrimazole vaginal pessary 1 thrice weekly	Dose **not stated**	Clotrimazolepessary is available in various strengths i.e. 100mg, 200mg and 500mg. The dose must be clearly stated in the protocol.
2	Fluconazole 100mg OD for 7 – 14 days	Only for **symptomatic**	Licensed dose for treatment of candiduria = 50 to 100mg daily for 7 to 30 days (Ref: BNF, SmPC).

		candiduria	NB: Asymptomatic candiduria rarely requires antifungal therapy unless it occurs in the setting of neutropenia, low birth-weight neonates, or urinary tract manipulation (Ref: UptoDate).
3	Candida can be resistant so be ready to seek microbiological advice	No issues raised	Nil

Third line	**Outcome of review**	**Consideration**
Fosfomycin 3g thrice weekly (only when combined with another agent)	Dosing frequency **does not reflect current evidence**	Licensed dose = **3g as a single dose** (in men, repeat dose after 3 days) (Ref: BNF, PHE) For lower complicated UTI (including recurrent UTI), **3g every other night for 3 doses** is suggested to be safe and effective in published studies (see Whittington Fosfomycin Guideline). For the prophylaxis of recurrent UTI, **3g every 10 days for 6 months** have been used in studies (see Whittington Fosfomycin Guideline).
	Treatment duration NOT stated.	See above.
	To be used as **single agent**	Further evidence needed for combination use as antagonism or indifference have been noted with some combinations (Falagas 2008).
Final recommendation re Fosfomycin. Within the LUTS clinic protocol to be used as a single agent only rather than in combination with other products.		

Fourth line	**Outcome of review**	**Consideration**
Ciprofloxacin 500mg BD. It should also be noted that it frequently achieves an acute effect but cannot hold control in the long-term so is really a short-term crisis medication.	**Treatment duration** NOT stated.	For complicated UTI / pyelonephritis, treat for 7 – 10 days.
Final recommendation re ciprofloxacin. This product can be used as part of the LUTS clinic protocol but only for a maximum duration of 14 days for treatment.		

Fifth line		
Ertapenem 1g IV over 30 minutes daily for 5 days.	**Restricted** antibiotic.	Microbiology advice must be sought before prescribing.
If penicillin intolerant: Gentamicin 7mg /kg OD IV for 5 days.	Require drug level monitoring.	Require renal function and drug level monitoring.

Additional comments re LUTS protocol

- The format of the protocol does not reflect the Whittington Health recognised template. The DTC require the protocol to be represented with the above review changes in the correct template available from Whittington Health intranet site.

- It was assumed that there was a distinct stepwise progression from the 1st line to the 5th line therapy following treatment failures – i.e. where one treatment option has failed, it is to be discontinued and switched to the subsequent treatment option.
- The antibiotic treatment protocol does not provide any information or advice on the duration of treatment, with the exception of the 4th line and 5th line treatment options.
- It should be noted that none of these antibiotic agents are suitable for combination therapy. The protocol should be made clearer to explain the distinct stepwise progression from first line drugs to second line and so on.
- In 2014/15, the annual antibacterial expenditure for Community Lower Urinary Tract Symptoms (LUTS) services was £212K, which equated to 45% of the total annual antibacterial expenditure for the whole of the Whittington Hospital.

DEPUTATION STATEMENT

on behalf of the Patients of the LUTS Clinic, Whittington Health

APPENDIX F

Macrobid Capsules 100mg B.P

Summary of Product Characteristics Updated 23-Sep-2014 | Amdipharm Mercury Company Limited

1. Name of the medicinal product

Macrobid 100mg Prolonged-release Capsules.

2. Qualitative and quantitative composition

Macrobid is a modified release, hard gelatin capsule containing the equivalent of 100mg of Nitrofurantoin in the form of nitrofurantoin macrocrystals and nitrofurantoin monohydrate.

3. Pharmaceutical form

The 100mg capsule has an opaque blue cap and opaque yellow body and bears the monogram “GS 100”.

4. Clinical particulars

4.1 Therapeutic indications

For the treatment of and prophylaxis against acute or recurrent, uncomplicated lower urinary tract infections or pyelitis either spontaneous or following surgical procedures.

Macrobid is specifically indicated for the treatment of infections when due to susceptible strains of Escherichia coli, Enterococci, Staphylococci, Citrobacter, Klebsiella and Enterobacter.

Most strains of Proteus and Serratia are resistant. All Pseudomonas strains are resistant.

Macrobid is not indicated for the treatment of associated renal cortical or perinephric abscesses.

4.2 Posology and method of administration

Route of administration: Oral

Adults and children over 12 years of age.

The dose should be taken with food or milk (e.g. at meal times).

Acute or recurrent uncomplicated UTI and pyelitis -100mg twice daily for seven days.

Surgical Prophylaxis - 100 mg twice daily on the day of the procedure and 3 days thereafter.

Elderly

Provided there is no significant renal impairment, in which nitrofurantoin is contraindicated, the dosage should be that for any normal adult.

See precaution and risks to elderly patients associated with long term therapy.

Children under 12 years

Macrobid is a fixed dosage and is therefore not suitable for children under 12 years

4.3 Contraindications

Patients with known hypersensitivity to nitrofurantoin or other nitrofurans.

Patients suffering from renal dysfunction with an eGFR of less than 45 ml/minute. Nitrofurantoin may be used with caution as short-course therapy only for the treatment of uncomplicated lower urinary tract infection in individual cases with an eGFR between 30-44 ml/min to treat resistant pathogens, when the benefits are expected to outweigh the risks.

G6PD deficiency (see also Section 4.6)

Acute porphyria.

In infants under three months of age as well as pregnant patients at term (during labour and delivery) because of the theoretical possibility of haemolytic anaemia in the foetus or in the newborn infant due to immature erythrocyte enzyme systems.

4.4 Special warnings and precautions for use

Nitrofurantoin is not effective for the treatment of parenchymal infections of a unilaterally functioning kidney. A surgical cause for infection should be excluded in recurrent or severe cases.

Since pre-existing conditions may mask hepatic or pulmonary adverse reactions, nitrofurantoin should be used with caution in patients with pulmonary disease, hepatic dysfunction, neurological disorders and allergic diathesis.

Peripheral neuropathy and susceptibility to peripheral neuropathy, which may become severe or irreversible has occurred and may be life threatening. Therefore, treatment should be stopped at the first signs of neural involvement (paraesthesiae).

Nitrofurantoin should be used with caution in patients with anaemia, diabetes mellitus, electrolyte imbalance, debilitating conditions, and vitamin B (particularly folate) deficiency.

Acute, subacute and chronic pulmonary reactions have been observed in patients treated with nitrofurantoin. If these reactions occur, nitrofurantoin should be discontinued immediately.

Chronic pulmonary reactions (including pulmonary fibrosis and diffuse interstitial pneumonitis) can develop insidiously, and may occur commonly in elderly patients. Close monitoring of the pulmonary conditions of patients receiving long-term therapy is warranted (especially in the elderly).

Patients should be monitored closely for signs of hepatitis (particularly in long term use).

Urine may be coloured yellow or brown after taking Nitrofurantoin. Patients on Nitrofurantoin are susceptible to false positive urinary glucose (if tested for reducing substances).

Nitrofurantoin should be discontinued at any signs of haemolysis in those with suspected glucose-6-phosphate dehydrogenase deficiency.

Gastrointestinal reactions may be minimised by taking the drug with food or milk, or by adjustment of dosage.

For long term treatment monitor the patient closely for appearance of hepatic or pulmonary symptoms and other evidence of toxicity.

Discontinue treatment with nitrofurantoin if otherwise unexplained pulmonary, hepatotoxic, haematological or neurological syndromes occur.

4.5 Interaction with other medicinal products and other forms of interaction

1. Increased absorption with food or agents delaying gastric emptying.
2. Decreased absorption with magnesium trisilicate.
3. Decreased renal excretion of Nitrofurantoin by probenecid and Sulphinpyrazone.
4. Decreased anti-bacterial activity by carbonic anhydrase inhibitors and urine alkalisation.
5. Anti-bacterial antagonism by quinolone anti-infectives.
6. Interference with some tests for glucose in urine.
7. As Nitrofurantoin belongs to a group of anti-bacterials and will have the following interactions:

Oestrogens: In common with other antibiotics, nitrofurantoin may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of oestrogen-containing contraceptive products. Therefore, patients should be warned appropriately and extra contraceptive precautions taken.

Typhoid vaccine (oral): Antibacterials inactivate oral typhoid vaccine.

4.6 Pregnancy and lactation

Animal studies with nitrofurantoin have shown no teratogenic effects. Nitrofurantoin has been in extensive clinical use since 1952 and its suitability in human pregnancy has been well documented. However, as with all other drugs, the maternal side effects may adversely affect course of pregnancy. The drug should be used at the lowest dose as appropriate for a specific indication, only after careful assessment.

Nitrofurantoin is however contraindicated in infants under three months of age and in pregnant women during labour and delivery because of the possible risk of haemolysis of the infants immature red cells. Breast feeding an infant known or suspected to have an erythrocyte enzyme deficiency (including G6PD deficiency), must be temporarily avoided, since Nitrofurantoin is detected in trace amounts in breast milk.

4.7 Effects on ability to drive and use machines

Macrobid may cause dizziness and drowsiness. Patients should be advised not to drive or operate machinery if affected in this way until such symptoms go away.

4.8 Undesirable effects

Respiratory

If any of the following respiratory reactions occur the drug should be discontinued.

Acute pulmonary reactions usually occur within the first week of treatment and are reversible on cessation of therapy. Acute pulmonary reactions are commonly manifested by fever, chills ,cough, chest pain, dyspnoea, pulmonary infiltration with consolidation or pleural effusion on chest x-ray, and eosinophilia. In subacute pulmonary reactions, fever and eosinophilia occur less often than in the acute form

Chronic pulmonary reactions occur rarely in patients who have received continuous therapy for six months or longer and are more common in elderly patients. Changes in ECG have occurred, associated with pulmonary reactions.

Minor symptoms such as fever, chills, cough and dyspnoea may be significant. Collapse and cyanosis have been reported rarely. The severity of chronic pulmonary reactions and their degree of resolution appear to be related to the duration of therapy after the first clinical signs appear. It is important to recognise symptoms as early as possible. Pulmonary function may be impaired permanently, even after cessation of therapy.

Hepatic

Hepatic reactions including cholestatic jaundice and chronic active hepatitis occur rarely. Fatalities have been reported. Cholestatic jaundice is generally associated with short-term therapy (usually up to two weeks). Chronic active hepatitis, occasionally leading to hepatic necrosis is generally associated with long-term therapy (usually after six months). The onset may be insidious. Treatment should be stopped at the first sign of hepatotoxicity.

Neurological

Peripheral neuropathy (including optical neuritis) with symptoms of sensory as well as motor involvement, which may become severe or irreversible, has been reported infrequently. Less frequent reactions of unknown causal relationship are depression, euphoria, confusion, psychotic reactions, nystagmus, vertigo, dizziness, asthenia, headache and drowsiness. Treatment should be stopped at the first sign of neurological involvement.

Gastrointestinal

Nausea and anorexia have been reported. Emesis, abdominal pain and diarrhoea are less common gastrointestinal reactions.

Hypersensitivity

Exfoliative dermatitis and erythema multiforme (including Stevens-Johnson syndrome) have been reported rarely.

Allergic skin reactions manifesting as angioneurotic oedema, maculopapular, erythematous or eczematous eruptions, urticaria, rash, and pruritus have occurred. Lupus-like syndrome associated with pulmonary reactions to nitrofurantoin has been reported.

Other hypersensitivity reactions include anaphylaxis, sialadenitis, pancreatitis, drug fever and arthralgia.

Haematological

Agranulocytosis, leucopenia, granulocytopenia, haemolytic anaemia, thrombocytopenia, glucose-6-phosphate dehydrogenase deficiency, anaemia, megaloblastic anaemia and eosinophilia have occurred. Cessation of therapy has generally returned the blood picture to normal. Aplastic anaemia has been reported rarely.

Other

Transient alopecia and benign intracranial hypertension.

Superinfections by fungi or resistant organisms such as *Pseudomonas* may occur. However, these are limited to the genito-urinary tract.

4.9 Overdose

Symptoms and signs of overdose include gastric irritation, nausea and vomiting. There is no specific antidote. Nitrofurantoin can be haemodialysed. Standard treatment is by induction of emesis or by gastric lavage in cases of recent ingestion. Monitoring of full blood count, liver function tests and pulmonary function, are recommended. A high fluid intake should be maintained to promote urinary excretion of the drug.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Nitrofurantoin is a broad spectrum antibacterial agent, active against the majority of urinary pathogens. It is bactericidal in renal tissue and throughout the urinary tract. The wide range of organisms sensitive to the bacterial activity include *Escherichia coli, Enteroccus faecalis, Klebsiella species, Enterobacter species, Staphylococcus species: (eg S. aureus, S. saprophyticus, S. epidermidis)*

Clinically, most common urinary pathogens are sensitive to nitrofurantoin. Some strains of *Enterobacter and Klebsiella* are resistant. Nitrofurantoin is not active against most strains of Proteus species or Serratia species. It has no activity against Pseudomonas species.

5.2 Pharmacokinetic properties

Clinical Pharmacology:

Each Macrobid capsule contains two forms of nitrofurantoin. 25% of the dose is macrocrystalline nitrofurantoin which has slower dissolution and absorption than nitrofurantoin microcrystals. The remaining 75% of the dose is microcrystalline nitrofurantoin contained in a powdered blend which on exposure to gastric and intestinal fluids forms a gel matrix resulting in a modified release of active ingredient over time. Combined these systems provide a clinically effective bactericidal urine concentration at therapeutic doses. Approx. 20-25% of the total single dose of nitrofurantoin is recovered from the urine unchanged over 24 hours.

Plasma nitrofurantoin concentrations at therapeutic doses of the Macrobid capsule are low, with peak levels usually less than 1 mcg/ml. Nitrofurantoin is highly soluble in urine to which it may impart a brown colour. Unlike many drugs the presence of food or agents delaying gastric emptying increases the bioavailability of the Macrobid capsule.

5.3 Preclinical safety data

None stated.

6. Pharmaceutical particulars

6.1 List of excipients

Macrobid Capsules contain talc, corn starch, lactose carbopol, povidone, sugar, magnesium stearate, gelatin and colouring agents (E104, E171, E132).

Printing ink contains Shellac, Propylene Glycol (E1520), Titanium Dioxide (E171), Black iron oxide (E172), Ammonium Hydroxide (E527) and Simethicone.

6.2 Incompatibilities

None known.

6.3 Shelf life

The expiry date for the product should not exceed 2 years from the date of its manufacture.

6.4 Special precautions for storage

Capsules should be stored in light and moisture resistant containers.

Storage temperature should not exceed 30°C (aluminium/ aluminium).

Do not store above 25°C (For PVC/ polyethylene/aclar/aluminium blisters)

6.5 Nature and contents of container

There are two pack sizes, one consists of 14 capsules and the other is a sample pack containing 2 capsules.

6.6 Special precautions for disposal and other handling

A patient information leaflet is provided with the product.

7. Marketing authorisation holder

Mercury Pharmaceuticals Ltd,

Capital House,

85 King William Street,

London EC4N 7BL, UK

8. Marketing authorisation number(s)

PL 12762/0052

9. Date of first authorisation/renewal of the authorisation

31/03/2000

10. Date of revision of the text

August 2014

Company Contact Details

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DEPUTATION STATEMENT

on behalf of the Patients of the LUTS Clinic, Whittington Health

APPENDIX G

Whittington Health NHS

Executive Offices
Magdala Avenue
London
N19 5NF

22nd October 2015

Dear Patient

Lower Urinary Tract Service (LUTS), Hornsey Central Neighbourhood Health Centre

I am very sorry to inform you at short notice that the clinic run by Professor James Malone-Lee at Hornsey Central has been suspended with immediate effect. This means that you should not attend the clinic for your next scheduled appointment.

We will be writing to you again within the next two weeks to invite you to attend an appointment at an alternative clinic to review your care. In the meantime, if you are unwell, or if you continue to have symptoms, please make an appointment with your GP.

This change has been necessary because of concerns about possible risks to the health of patients associated with some of the antibiotic prescriptions given to patients through this clinic, and the possibility of unwanted side-effects. It is likely that some of these possible side-effects may already have been discussed with you in the clinic. However, if you have any concerns about this you should discuss this with your GP.

I am advising your GP and local Clinical Commissioning Group of these actions. I am also advising your GP of the possible alternative services that your GP may wish to refer you to.

If you have any queries that have not been addressed in this letter then you can call the Patient Advisory Liaison Service (PALS) on 0207 288 3876. The PALS office is open Monday – Friday between the hours of 10am – 12pm and 1pm – 3pm.

Yours sincerely,

Dr Richard Jennings

Executive Medical Director

Whittington Health

DEPUTATION STATEMENT

on behalf of the Patients of the LUTS Clinic, Whittington Health

APPENDIX H

Patient Helpline and Communication - some examples of no responses, poor communication etc, collated from the Patient Facebook group

Factual Notes:

Patients confirm the Helpline was not set up until 2 weeks after the clinic closure on 21 Oct 2015. The experiences below are only a sample of those provided by patients. There are many more stories of failed call backs, conflicting information, poor or no communication, and lack of medical/clinical care.

1. **Administrators of the Patient Facebook Group:** On 9/11/15 the Facebook group was asked by Whittington to collate patients who are unwell, flaring, have had to go to hospital etc. around 50 people asked for urgent assistance due to increasing pain, kidney pain, blood in urine, chills, fevers, concerns over antibiotics running out. As at 17/11/15 one was contacted as result of submitting this information 17/11/15.

2. **AT** (whose 6 year old daughter is a Patient): Last night (10/11/15) I had a call from someone who works in the Medical Director's office at the Whittington. She said she would get a clinician to ring me today. I said that I first called the helpline on Thursday (5/11/15) and was told we were marked as urgent, but still hadn't received a call. Said that A had deteriorated significantly since then, listed her symptoms over the phone. She impressed on me the need to go to A&E if A deteriorated further. I said I would of course do that, but unfortunately A&E do not have the expertise to help with poly microbial and antibiotic resistant infections and A would need treatment from a clinical specialist. I also asked why my emails had not been responded to and my calls for medical help hadn't been answered. I also received an email, in response to a request for urgent medical advice for A, giving me contact details for a COB patient support forum and also the Facebook site set up by Patients, with my own email address as a contact. I stated I was shocked that I had been asked to contact myself for support and advice. I asked her to please find out how this had been able to happen in lieu of proper medical advice. There was silence. She said the patient helpline is there for medical advice; I said it was just a note taking service, no one had received a call back, even medical cases marked as urgent. The helpline wasn't working, even the staff running it had admitted this. I said the clinic should never have been closed without a proper medical intervention/service in place beforehand and it was vulnerable patients who are suffering. I also told her that I was aware of another patient that had been admitted into hospital via A&E as an emergency admission.

3. **CL**: 14/11/15 Sadly, as I had been expecting my infection has got worse. Had seen GP who couldn't help, and calling Helpline for past 2 weeks - no call back and then today in agony. Had to go to A&E as instructed by GP. Urine showed positive for infection. Finally offered 7 days of Amoxicillin (which I know will do nothing). Asked what I should do if this doesn't work - go back to GP.

4. **NS:** 10//11/15 I told them the infection had spread to my kidneys and was in a lot of pain. That A&E couldn't help me. Not a single call back.

5. **AT:** 9/11/15 I wrote to PALS on Wednesday night (4/11/15). I have not had a response and they are supposed to reply within 48 hours I believe. I was also meant to receive a call back from a pediatrician and I never did. It was marked as urgent.

6. **GH:** I have called 10 times and still received no call back. I said I was very ill and required urgent help.

7. **CL**: I called the 'Helpline' last Tuesday (3/11/15) in distress to say I'd run out of my flare meds and my GP can't prescribe - I was told that I was marked 'urgent' and that someone should called me back ASAP probably that day - that was a WEEK ago and no-one has called.

8. **HW:** I phoned and left a message last Thursday (5/11/15). No call back. I've had no reply to my formal complaint. I did get a consultant call back Julie Andrews who wanted to reassure me that urgent measures were being taken and I should go to GP for antibiotics.

9. **AF:** My mum (who rang on my behalf) received a voicemail from Lisa Brown of the PALS line saying that she has 'looked into my request to have a copy of my medical records', and that all I need to do is to make a request to the LUTS helpline e-mail and then they will fax notes to my GP..... I have already done this, FIVE TIMES... Not a word in response and no notes sent. I have also, as of this morning, apparently being added to Fiona Isaacson's list of people to 'urgently' contact as I have stated that I'm having side effects. I also left a voicemail with PALS this morning asking for a call back. No call back.

10. **NS**: never received any communication about the clinic suspension. She says she would not even know about the closure if it wasn't for the Facebook group.

11. **AT**: 9/11/15 I was told today by the lady on the Helpline, that: *"the Helpline wasn't working and no emergency services had been provided for patients*."

12. **NS** 9/11/15: Linda told me I'd be called by a microbiologist by last Friday (6/11/15). No call.

13. **KRIL**: 9/11/15 I was told that I would get a phone call by the end of today. I never did.

14. **Anon:** 10//11/15 Numerous Patients noted that the “Communications email address” supplied for patients was incorrect.

15. **NS**: I called again today 9/11/15 and Liz said she'd pass it on to the manager and I'd get a call today. Liz even called back near to 2pm confirming I'd get a call. No call again.

16. **SM:** Phoned the Helpline on the day it opened (2/11/15), promised a call back "should be same day" still haven't had a call.

17. **LR:** 9/11/15 I have not yet received a call back despite ringing three times in tears last week.

18. **JG:** I called the Helpline on 5/11/15 and was told I would receive a call back from a gynecologist , microbiologist or urologist. As of 17/11/15 I am still waiting.

19. **NS**: 9/11/15: The first day the helpline opened, last Monday, I called the hospital to either put me through or give me the number. The receptionist said there's no such helpline, and then she asked if I was the woman she spoke to earlier (I wasn't) as she previously told another woman the same day that no such helpline existed. Also she wouldn't give her name which she should. I told PALS about it and they said it was wrong.

20. **JG**: complained to PALS making a formal complaint . As of 17/11/15, no acknowledgement or reply received. It should be acknowledged within 48 hours.

21. **LDM**: called helpline 5/11/15. No response.

22. **OP**: Generic patient letter sent to my husband’s email address instead of mine.

23. **BMB**: I’ve received absolutely NO reply to my email to the Helpline. I sent it last Wednesday (4/11/15), got an immediate out of office stating I would get a reply within 2 working days. I also called the helpline on the first day. Got answer phone. Called back several times more before getting though to Maureen who failed to find me on the system! Eventually found me but was unable to answer any of my questions. Told me I would receive a call back, I've not had one.

24. **BMB**: I've also emailed the Helpline, Dr Jennings & Simon Pleydell, no response from anyone.

25. **SP:** Dr Jennings' first letter includes several predetermined questions, one of this is "my medication is about to run out, what should I do?" and the answer for people who "normally get a repeat prescription from the LUTS clinic itself" is: "you should telephone the LUTS patient helpline to discuss this." I called the helpline twice and

both times the nurse told me that I should go to my GP. I tried to tell them that the letter says otherwise so they said that I can try and wait for a reply from one of the consultants but they won't be able to prescribe the antibiotics.

26. **ECJ:** I was told I'd get a call back but then also that it's possible I'd get nothing because I'm a private patient so that's a bit of a contradiction.

27. **AF**: I've sent 4 e-mails to the Helpline, starting the day it opened (2/11/15). Instead of e-mailing back they rang me (after my 2nd email) and left a voicemail asking me to call them back. I e-mailed saying that I have received the voicemail but that unfortunately I can't ring back due to me working 9 - 5, so please can they reply to my original e-mail. I emailed again about a week later when I still had no reply. Yesterday (9/11/15) they sent me the generic letter from Dr Jennings but didn't address any of my questions. Among other things, I've been requesting access to my clinical notes, which I legally should be given (Data Protection Act) on request. Still nothing.

28. **CL**: The 2nd email from Dr Jennings (with the 4 page letter giving the number of the 'Helpline') appears to have only gone out to people who complained - the lady in PALs sort of admitted that when I turned up in person last week.

29. **CL**: The invitation email advising of the Patients's meeting at the Whittington this Thursday (12 Nov) seems to have been really hit and miss - some people on here got it and others didn't - my friend not in this group didn't get it at all - the first she heard was when I forwarded it to her - this is NOT FAIR - ALL clinic patients should have been allowed the choice to air their views not a random selection.

30. **JK**: Most patients will only have received the first letter notifying them of the clinic closure. That's the only letter I have received. I've only had the email doc because I've complained so many times. Nothing about the meeting on Thursday. As you say ALL patient's should be invited. There is no consistency in their communication. Complete shambles.

31. **LH**: Letter to private patients resent today (10/11/15) (dated 23rd Oct) to call Prof or his private secretary if we have any questions about the closure. How can we do this?

32. **AC**: Rang helpline Tuesday 3rd November saying I needed my medications. No one has rung me back. 'Letter regarding Luts Clinic' only received it yesterday by email (9/11/15).

33. **LH** No replies to any of the emails I have sent.

34. **JGrl**: 10/11/15 I only received a reply to my letter to Jennings, sent immediately after the closure of the clinic, yesterday! It was only a standard reply. I bet he didn't bother to read my story! Very poor.

35. **NS** 10/11/15 I just spoke to Linda, she told me that there's only her manning the phones, so that's why it's difficult to get through.

36. **FB**: 10/11/15 I called on day one (2/11/15) and was told I'd be called back that week (last week) I've called repeatedly. Liz admitted yesterday that the consultants have only started calling THIS week.

37. **HW**: I wrote to 8 of the trust board members individual letters including the Acting Chair and I received a letter naming them all from PA to Simon Pleydell saying the letters had all been sent to PALS for processing"! As of 17/11/15 no replies have been received.

38. **CM**: Called LUTS Helpline on the first day it became live (2/11/15) and was told I would be contacted by the Whittington that day. No call to date. No response from any emails to PALS etc. Generic email from Jennings saying I would receive appt for Whittington Team. I have received nothing of course.

39. **DG:** I've called 3 times, once to PALS and was told Dr Jennings was in a 'meeting" (which he remained in for the whole week by the sound of things). I was told he would call me back - no call. Then called the Helpline line twice. No answers to any of my questions . No letter until TODAY (10/11/15) from Whittington trust telling me the clinic had closed.

40. **SY:** I've received an email today from the hospital about the private patient service. I haven't been a private patient of Prof's for over a year now. Quite why I get this and none of his current private patients is a mystery.

41. **Annon**: I had to go to the out of hours GP last Friday. Blood in urine again. I called the helpline today and emailed them over the weekend. Liz said she'll ask someone to call back today.

42. **BMB:** My sister received the standard email from Jennings advising her of the closure of the clinic and how she could get support from the FB group. My sister isn't & never has been a patient of PML. She did however send Dr Jennings an email, he clearly didn't read it thoroughly enough.

43. **VM**: 10/11/15 Called again today. No one called back from the middle of last week. My request for a call back has been taken again and this report is given to management (directors) about all our calls etc.

44. **NS**: 10/11/15 I called again today and spoke to Linda, again I was told I'd be called back today. No call. Will call again tomorrow and email again tonight.

45. **DF** 10/11/15 Called last Monday (2/11/515) still no reply.

46. **LJ:** I turned up to clinic on Monday (9/11/15) for scheduled appointment, before finding out the Prof's clinic had been closed. Received NO communication prior to this and have checked e-mail and spam thoroughly.

47. **MF**: The helpline has a busy tone every time I call - I have emailed but had no reply.

48. **NS**: I called the helpline again (11/11/15) to tell them I've had no call. Spoke to Maureen who apologised and said I should have been called and she will pass on another urgent message.

49. **Anon**: Yesterday it took me 15 minutes to get through. I was calling every 15 seconds and either getting the answer phone, which I left a message on first time around or engaged tone. It's like this every time you ring.

50. **Anon**: Health Ombudsmen states they will not deal with patients complaints until they have been through the Whittington complaints process but patients are not receiving replies so cannot take their complaints through the process.

51. **AH:** 9/11/15 I have been having a bad flare and have been admitted through A&E.

52. **KRIL:** I again rang LUTS helpline this morning for the 4th time just to drive to them how badly people are reacting healthwise to the closure. I told them people were deteriorating and that we need the clinic re instating asap. I was almost in a wheelchair last year, and I refuse to go back to that.

53. **AF**: 9/11/15 I've just read the letter from Jennings sent via the PALS address. I have sent 3 e-mails to this 'helpline' address since the clinic's closure and I have had absolutely no acknowledgement or response; just this letter. I actually broke down in tears from sheer frustration after reading.

54. **EM** Called Helpline, spoke to a lovely sympathetic lady who listened but basically said they were simply collecting information. I was told I would be called back but the main point of the helpline was to gather information.

55. **NS** 12/11/15 Just spoke to Maureen on the helpline she said there's now no call backs being done by any of the consultants. So why have we been told everyday that someone will be calling us?

56. **MS** The consultant who called from the Helpline said I have to contact my antenatal obstetrician or GP to prescribe me the antibiotic further as she can't do it. GP gave me 7 days course and obstetrician I have just seen sent me to my GP although GP can't help. I called the Helpline back, spoke to Maureen and she will pass message to somebody to call me back again.

DEPUTATION STATEMENT

on behalf of the Patients of the LUTS Clinic, Whittington Health

APPENDIX I

PATIENT STORIES AND IMPACT STATEMENTS

(collated from the Patient Facebook group)

Patient Impact Statement

I have a long history of urinary tract infections starting 15 years ago (2000) when I was 20 years old and first became sexually active. I had no bladder problems before this. I was treated by the GP with a short course of antibiotics but I continued to suffer with recurring infections.

I was referred to an urologist (2005) who assured me that a cystoscopy and bladder/ urethral stretch would stop my infections. This was not the case. After treatment I had a huge increase in bladder pain and an acute infection. The urologist was not helpful. I was told there was no further treatment he could offer and I was discharged back to my GP. It took approximately six months for the bladder pain to subside and I credit this treatment with increasing the condition's severity. My GP referred me to an urogynaecologist who did some investigations but she could find no cause for my recurrent infections and could offer no treatment. My GP suggested I try a prophylactic dose of antibiotics which did decrease the number of infections per year for a short time. It also made it possible for me to have sex again without getting an acute infection every time. In April 2010 I developed a severe infection that did not respond to the numerous short courses of antibiotics I was given.

I was now so unwell with severe bladder pain and frequency that I had to give up my job as a Marketing Director. I educated myself on the condition and sought both traditional medical help and alternative therapy. I saw a number of urologists who all suggested invasive procedures recommended for IC patients such as urethral dilation, bladder stretch and bladder instillations. I was also offered medication for over active bladder and botox injections in the bladder to help with frequency. I was very wary about having these invasive procedures as the original bladder/ urethral stretch had made the condition worse.

In 2011 following emergency admission to hospital I was diagnosed with urinary retention and damage to my right kidney.

The final urologist I saw did another cystoscopy. He advised that any invasive procedures were unlikely to help my chronic infection. He prescribed a longer course of antibiotics for six weeks resulting in minor relief from symptoms. However it did not clear the infection and he could not offer any further treatment. He referred me to Professor Malone-Lee.

I first saw the Professor in April 2012 and began the long term antibiotic therapy. I finally started to see an end to the twelve years of unrelenting bladder pain. I was impressed by him and his real understanding of this debilitating condition. He told me that I had probably had a chronic infection for a long time, perhaps since I first saw my GP in 2000. He explained how bacteria can embed into the bladder wall and are protected from antibiotic attack and what is needed is much longer courses of antibiotics.

Within two months of starting treatment I was 90% better. It has been a long journey. I had to stop an antibiotic that worked very well due to an allergic reaction. This was handled promptly by the clinic and was not serious but it took a while for another antibiotic regime to work as well as the first one. Eventually my symptoms were under control again and this was reflected in the clinic's regular urine checks.

I cannot stress enough what a negative effect this condition has had on the course of my life. I have had to fight for treatment and have personally spent a lot of money seeing specialists privately to try to find answers and an end to my pain. Whilst I have found some specialists to be sympathetic, I have been told that I am a difficult case and they have not seen a patient who gets so many recurring infections. GPs were baffled, particularly in later years, when I would present to them with what appeared to be an acute

infection – blood in the urine, leucocytes and pain. They would send a urine sample to the lab but no infection would be found.

I have always known that my condition was caused by some sort of infection. I do not fit the profile for an IC patient (specialists have agreed with this) plus I have had many urine cultures showing bacteria. It has been incredibly disheartening to see so many specialists who have only offered treatment to alleviate symptoms rather than a cure.

I have always trusted the Professor as chronic infection is his specialism and life's work. He is always available on email to answer personal concerns. He has given me back my life. In the three years I've been in treatment with him I have managed to go back to work, get married, have regular sex and I have recently had a baby. None of this would have been possible without his treatment. I no longer suffer with ongoing bladder pain, frequency or urgency. I have had an ultrasound and my urinary retention has resolved. I still experience dull urethral pain and occasional mild flare ups which the Professor manages with a temporary increase in my antibiotic dose. The long term antibiotics have had no ill effects and I was able to stay on them during pregnancy.

My future looks a lot brighter thanks to the Professor. In particular I am so grateful for the treatment I received during pregnancy. I was monitored fastidiously and had appointments every month. Had I not received treatment from the Professor I would never have been able to have a baby as sex was impossible due to the pain and infection I would get every time. I believe that I will be off the antibiotics soon and I feel confident that if I was ever to have bladder problems again the Professor and his team would be able to help.

Patient Impact Statement

About three years ago, I had what felt like a normal bout of cystitis, unbearable pain in my bladder that feels like a thousand bees are stinging your bladder at the same time. I had antibiotics on standby as I got cystitis quite regularly and after a three-day dose of antibiotics it normally went away. This time, however, the pain didn't go away, it got worse and worse. I called my GP and they prescribed me painkillers. I sat in my bed for weeks, rocking in agony and getting increasingly hysterical. I continued to call my GP daily, who, after about a month, eventually referred me to a urologist. This took 12 weeks. But I thought at this point that I would go to the urologist and they would know what to do. So this was keeping me going.

When I went to the urologist, I began to explain what was happening but before I could even say what I felt like, she had written on a piece of paper 'recurrent cystitis' and said I needed a cystoscopy. I explained that this was not recurrent cystitis, it was just cystitis, with pain 24 hours a day, every day. She ignored this and insisted I needed a cystoscopy. I asked how this would help and what the varying treatments would be according to what they found. She shut me down and said that this was what I needed. I was in tears, I couldn't speak and was ushered into a room to give consent to the surgery. I signed, with apparently no other options. Again, I thought the urologist must know best and waited for three months for my cystoscopy. After the operation, I got a call saying 'good news, it's not cancer'. I didn't care whether it was cancer or not, I was in constant pain and I needed a solution to this. I didn't even get an acknowledgement of this. He'd given me my results. Job done. My mental state was deteriorating rapidly. I had now taken months off work, I was visiting A&E regularly for intravenous morphine. I was also visiting various NHS consultants that I'd asked to be referred to. One consultant suggested that the pain may have been caused by eating too much red meat...another asked whether I had considered that I might be subconsciously in need of attention from those close to me, so imagining the pain...

I was now suicidal. I had visited my GP and consultants countless times and all they could offer was mounds of useless drugs, more useless tests and a referral to CBT. I took the drugs, endured the painful and humiliating examinations and tests, started and finished CBT, and was still in pain and suicidal. I was sitting day in day out rocking in pain in the same spot on the sofa, scouring the internet for treatment ideas. This is when I came across Professor Malone-Lee. I emailed him. By this point I was no longer consulting my GP, for fear of being further belittled and patronised.

At my first appointment with the Professor, he actually listened to me. He was the first person to understand how I was feeling. I was skeptical about his treatment regimes at first; having been given all sorts of different pills that did absolutely nothing. But what he explained to me made sense; he took the time to explain how and why the treatment would work. No one had yet been able to do this. When I had asked tricky questions previously, urologists and GPs had dodged them and skirted over the facts but the Professor's explanation made complete sense. The first months of treatment were rocky; there were times when I thought that my pain was getting worse. Then after about three months, the pain started to reduce, slowly, but it was definitely changing, there were times that I could get out of the house without fear of being in such agonising pain. Then after about 6 months, the pain improved significantly, I began a phased return to work. Despite ups and downs, for which I rely heavily on the Professor to tweak my regime, I have been back at work for a year and a half.

Now, under the assurances of the Professor and the NHS, that I would be able to continue my treatment remotely, 6 weeks ago I left London to move to a developing country. I have diplomatic status so am still under the duty of care of the NHS whilst I am here. When I received the letter about the suspension, I was terrified - the treatment that I have been receiving, that is so specialized, that allows me to function, will be taken away just like that and I am in a developing country with one of the most rudimentary health systems in the world.

On Saturday, my mental health deteriorated significantly, I am again, left with no control over my future health. The NHS is again, dictating what is best for me. I have gone back to suicidal thinking. It is simple, if the Professor is not there to provide his specialised treatment; I have no chance of any quality of life whatsoever. So what's the point?

Patient Impact Statement

After repeated attacks of cystitis when I was younger I had an attack that did not appear to go away. Amazingly my urine tests were now clear. No one knew what to do with me as I still had vicious symptoms and there was no reason for them, apparently.

My GP could only offer to refer me to a psychiatrist, as clearly it was all imagined! He also suggested that I was only claiming to have symptoms to upset my mother! My relationship with my mother was fine and I have never visited the GP or been ill before. Of course my mother was upset that I was unwell, but there was no reason to suggest that I was faking an illness to upset her! The GP told me there was no such thing as a painful bladder in the absence of a positive urine test.

I went to see a total of six different urologists over the years, all of them private as I had medical insurance from work. I ended up having four cystoscopies, each one by different urologists, a laparoscopy and a bladder stretch. Each of which hugely increased my agony. After one cystoscopy I was in so much pain I was screaming and rocking on the floor with stabbing pains in my bladder worse than labour. I saw a private GP (I had to go to a private GP as my NHS GP was not interested in helping me). But this private GP, when referring me to a certain specialist said "I'll refer you to Mr X, he needs the work!" I did agree with NHS GP when I told him what had been happening, he pointed out that these urologists had exploited my medical insurance as there was no need to perform repeated cystoscopies on me. None of the cystoscopies found anything. I was told that the bladder stretch made 90% of patients better. It did nothing for me but increase my pain and since then I have met women who have also had the bladder stretch and it has helped no one so I don't know where the figure of 90% comes from.

After my extensive experience of top urologists I've come to the conclusion that they know nothing about my condition, they make a lot of money from doing procedures which don't work on people like me, and too many urologists are rather disdainful of female bladder problems, and see this area of their work is rather "unsexy". The old-fashioned view that when a woman complains of women's health problems she is neurotic or hysterical seems still to be lurking there in the background. I never felt listened to and the attitude of the medical profession was arrogant – if their tests were negative then there was nothing wrong with me. I have since learnt the truth from the professor that no test is superior to a patient's symptoms and the patients symptoms are the best indicator

of disease. Eventually I became aware of the condition "interstitial cystitis". After one terrifying attack when I was screaming in agony, in **desperation, I went to casualty for the first time**. I mentioned to the nurse that I thought it was interstitial cystitis and she came back and very sneeringly said "the registrar has never heard of interstitial cystitis".

The most disturbing experience I had with a urologist was only last year. What happened will be hard for you to believe. This private urologist told me that "the urethra runs through the vagina, effectively you wee through your vagina"!! Afterwards I thought I must have misheard, but my husband was with me and he clearly heard this too. He then diagnosed me with a condition which does not exist "inflammatory cystitis" and I have his letter with this diagnosis. The name of this condition does not make sense because translated it is "inflammatory bladder inflammation". He then booked me in for the wrong ultrasound test, luckily I realised they had made a mistake and cancelled the test. Of course I was not going to go back to him. When he realised this, I received an email from his secretary saying I was very lucky that she had booked me in for a cystoscopy with him and gave me the date! I had never discussed cystoscopies with him other than to say I had had four and would never want one again! I wrote back saying I was not going to do it. Week or two later they wrote to me again saying they now had to back my urine test results (I knew they'd had those results for over a month as I had also requested a copy direct from the lab) and on the basis of these tests I must have a cystoscopy!

The week after I saw this terrible urologist I went to see Professor Malone Lee. The contrast could not have been more marked. My husband and I were completely blown away by how amazing we thought the professor was. Finally I found someone who I believed in and instinctively I knew he was right. Not only is he the only person who can help me with my chronic infection he is a deeply ethical and caring man. He works hard on his innovative work in the face of opposition from the "establishment". I am convinced that in decades to come his way will be the only way to care for patients with "IC". I feel that in future decades people will look back in horror at the way the millions of people with this condition were misdiagnosed and treated, now knowing that as a professor believes that our symptoms were caused by ingrained UTIs. The

professor is the first person to give me hope and although I am a hard case as I have had the infection for a long time I am making progress and my results show that hopefully I have turned a corner, and will finally progress to a full recovery.

For the first time I have had five nearly symptom-free days for the first time in a year. This correlates to the last urine test I had with the professor where my pus and epithelial cells have dropped dramatically. I could see that the professor was excited and thought finally we had the "bite" – the name he gives when he realises that we finally got a grip on the infection. I could see the excitement on the professor's face – he is truly an exceptional Doctor in The level of care and compassion he offers his patients and is genuinely thrilled when they start to improve and be cured. An experienced patient who eats sleeps and breathes this terrible condition and who has seen many many specialists, develops a strong instinct on what treatment is right for them and who is an intelligent and caring doctor. Professor Malone Lee is just this person – all other urologists and all the doctors I have seen have not come close and some of them were beyond shocking.

Lastly I want to make it clear how terrible and distressing this condition is. It is living with permanent chronic cystitis plus more distress and pain. Many patients including myself have contemplated bladder removal and suicide at times as I just cannot live on with the pain. My pains are ever-changing from acid burning to sharpness – a common feature with people with my condition. It is like I'm going through a series of tortures every day.

Patient Impact Statement

I'm 38 years old with two children. Since I was about 6/7 I remember experiencing occasional urine infections which were treated fairly easily with anitbiotics. Following both my pregnancies I developed more persistent infections which took longer to resolve and were resistant to some antibiotics - although both resolved eventually with normal courses of treatment.

My current infection developed out of the blue. I was woken by the severe burning sensation and drank lots of water to try to flush it out. This was unsuccessful so I saw the out of hours doctor who prescribed a one off dose of fosfomycin(at that time I was living in France). 48 hours later the infection returned with very strong and steadily worsening symptoms. I was prescribed ciprofloxacin, but 5 days later was hospitalised in severe pain for tests to rule out any kidney stones. I underwent a contrast CT and ultrasound which found nothing so was released, given an extended course of ciprofloxacin and told that hopefully it would clear up. However symptoms never fully resolved and at the end of the course, things got worse again. I saw a Urologist who prescribed cephalexin for 21 days in the hope this would work. Again although it lessened symptoms they hadn't totally cleared up and when I stopped that treatment it recurred. At this stage I had now developed further symptoms: on top of constant burning and urethral pain I was getting bladder pain, urgency and also developing some kidney pain. I was running a low grade temperature as well and feeling really ill. I was unable to work, or look after my children. I was utterly desperate as the level of pain and discomfort was such that I was beside myself. No painkillers even touched it and I was unable to sleep or rest.

Eventually I was admitted as an emergency case for pain relief and further investigation. A specimen showed clear signs of infection and I was put on IV antibiotics. These resolved the pain and burning sensation almost immediately. However, things didn't feel 'right' - the flow or urine was slow and felt like the urethra was still constricted in some way. 48 hours after leaving the hospital symptoms returned. I underwent a cystoscopy to rule out interstitial cystitis, but my bladder looked entirely normal and all tests were normal. The consultant concluded that this was some kind of chronic infection, but admitted he was baffled and did not know what to do. By then I had been ill for more than 8 weeks.

As someone with a medical background, I turned to research and noticed several papers mentioned Prof Malone-Lee. I soon found he ran a clinic in north London and was able to arrange an appointment. He examined my urine sample microscopically and saw high levels of epithelial cells (more than you would see for a contaminated sample) and pus cells - clear signs of infection. He was able to give me a clear diagnosis for my symptoms and begin to treat them - although he warned me treatment was complex and would take some time. He assured me that the vast majority of his patients were able to come off antibiotics following several months of treatment and then remain antibiotic and symptom free. I began treatment taking Azithromycin. Over the coming months when I saw him he rechecked my urine and we saw a clear improvement in levels of the epithelial and pus cells with a gradual reduction. Symptoms also vastly improved - immediately reducing, although there were occasional flares when things were worse. These flares also became less severe. I was able to immediately (within days of starting treatment) return to work and to my normal routine.

Following ten months of treatment my tests were very close to normal and we began to talk of stopping antibiotics. However, my last test showed a slight resurgence in pus cells and Prof Malone-Lee was concerned that we had not totally eradicated the bacterial infection. He therefore added nitrofurantoin to my prescription and we agreed to review things mid November. He remained confident I would be able to stop antibiotics very soon and would be symptom free.

With the abrupt suspension of his clinic I am unable to assess how things are progressing. I risk having to stop treatment prematurely and risk the return of my infection, as well as the increased risk of it becoming antibiotic resistant due to unfinished treatment. I have visited a local urologist who is sympathetic but has no experience of treating similar conditions successfully. She shares my concern about the infection returning and worsening. Prof Malone-Lee's clinic is unique in his expertise, experience, and most

importantly in his successful treatment of such patients. In the absence of his expertise, all my urologist is able to offer me is an attempt to manage the pain and discomfort (should it recur on stopping the antibiotics) as a chronic condition. I cannot emphasise enough that this is not going to be an acceptable course of action - the pain I was in was so severe I could not function at all, and was developing worsening symptoms. Untreated I risk developing more serious bladder problems and possibly long term damage to my bladder or kidneys. This is the greatest possible contrast to the situation I was in before the clinic was suspended where I looked forward to very soon being able to come off antibiotics having found a complete cure to my infection.

Patient Impact Statement

I am a patient who has profoundly benefitted from his treatment. I am a 37 year old medically qualified woman. I initially suffered from cystitis with gross haematuria in my early 20s and treated with the standard short courses on oral antibiotics.

Unfortunately I was diagnosed in 2005 with SLE, in 2006, with antiphosphlioid syndrome (APS) and in 2008 with CVID (common variable immune deficiency, with no B cells and little IgG and IgA.

I have continued to have UTIs which were probably mistreated as 'renal serositis' for some years. The infections trigger my SLE which can be severe. It is therefore very difficult to establish cause and effect especially as my immune deficiency means I do not mount an acute phase response with no CRP rise. **Things got determinedly worse in 2013-2014 I spent 16 months in St Thomas' Hospital** with recurrent severe sepsis. I was treated for multi drug resistant organisms that were cultured including: Pseudomonas, Vancomycin resistant enterococcus (VRE), E.Coli with multi resistance Proteus

I was treated with ever-increasingly less used IV antibiotics. Every time I was discharged I became unwell with days/weeks and was re admitted to St Thomas' Hospital, usually through Resus in A&E with a rising lactate and a systolic BP of 50/. Over the period I had: Meropenem, Vancomycin, Amoxicillin, Amikacin Ciprofloxacin Linezolid
Coamoxiclav

I was getting to the end of St Thomas' ability to manage me and my Immunologist at the Royal **Free who looks after my CVID told me of Professor Malone Lee and his work. I was told he was my 'last and only hope'.** When I first met Prof in July 2014, I was not in a good state, coming straight from being an inpatient at St Thomas'. However he reassured me he had treated patients like me before and although it might take some time, I would get better. Having just spent 16 months as an inpatient this was something I needed to hear!

I was slowly weaned off the IV antibiotics from July to January 15 under the watchful eye of Prof and my immunologist and supportive GP. In January I started an oral regimen of nitrofurantoin, azithromycin and cefalexin. I took these at various points as directed my Prof in whom I had complete confidence.

I have been trained in the traditional medical way at Nottingham medical school graduating in 2002. I was sceptical and concerned about the long term usage of antibiotics especially around resistance. However, Prof was able to show me compelling research that he had considered this and it was not a risk. He discussed side effects with me and I understood the symptoms I would need to report should I develop them. **Also please remember I was desperate. I had had ongoing pyelonephritis from 2013-2014 and followed traditional medical routes yet continued to develop severe sepsis secondary to multi drug resistant pyelonephritis every few weeks off antibiotics**.

The treatment had been a resounding success!

I have not had a SINGLE admission in 2015 for pyelonephritis or any UTI. I have had two culture proven UTIs in 2015, and both were normal infections and NOT multi drug resistant- this is despite being on long term antibiotics from Prof. He monitored me meticulously- he did fresh urine microscopy every visit and adjusted treatment accordingly. His team were always available and responded very quickly within an hour or so if I was unwell. Prof gave me his mobile number so that if I was septic he could be contacted. Luckily I did not need to ring that number.

This treatment has literally saved my life. How many more severe septic events could I have taken at that time? My kidney function has also been affected by my resurrect sepsis and AKI/pyelonephritis so that my GFR has gone from 120 in 2012 to 51 this month. Clearly I need to prevent sepsis from my chronic UTI**. Moreover, I have resumed work - full time- the first time in a decade**. This has been the effect that I

attribute fully to Prof's treatment. To remove the acute flare ups of the chronic infection means my SLE is better and I am able to receive more Ivig for the CVID thus preventing other infections. It seemed the cycle had been broken.

Now however, I am very concerned for my future. The abrupt removal of this clinic had left me without medical cover for my chronic UTI. Who is going to take responsibility for my ongoing care and prevent the recurrent sepsis I suffered?

Patient Impact Statement

Numerous visits to the GP didn't bring any answers for pain around rib cage, antacids and pain killers were prescribed. Nothing helped. Three days before Christmas my pain was dreadful, my son insisted I go to hospital. I'm eventually admitted after many hours in A&E and oramorph. They perform emergency ultrasound scans of gallbladder/kidneys. Lots of bloods taken, and urinalysis. I'm told all is normal, however they keep asking about my 'waterworks' I tell them I don't have any burning so I think everything's ok. They give me 2 lots of antibiotics to take and I'm discharged, their busy, it's Christmas. Three weeks later and I'm still in dreadful pain. I've been back & forth to my GP, she runs more bloods. ESR is always raised. Feeling so bad, make an emergency appointment with GP. She takes one look and sends me straight back into hospital, no arguments. I'm in for 5 days; they complete the CT of my kidneys on day 1, talk a lot about performing a more detailed MRI I'm discharged after they decided my pain must be linked to my chronic back condition. They refer me back to the pain clinic that I was discharged from the previous year!!!!!. They send a pain clinic nurse to the ward to speak to me, I know her well. She asks if this pain is anything like my normal back pain or a new pain. I tell her it's a new pain, completely different, and that I've been trying to explain but they won't listen. She says she understands, and I don't need to see the pain clinic, she can see this is something new. I'm now starting to get a vague pain in my pelvic region. This pain develops over the coming weeks. I start visiting the loo more frequently and wake 2/3 times a night to pee, not being able to get back to sleep in-between as my bladder hurts and still feels full. I attend my endoscopy appointment. I'm promised sedation by the admitting nurse as I'm very nervous. I go to theatre; the doctors tell me NO sedation allowed. I'm horrified. I beg & plead, no good, they practically sit on me. I feel violated and traumatised by the experience, I'm told there's a slight area of gastritis, there've taken a sample. They give me a further 2 lots of antibiotics just in. I complain to my GP and advise her I'm not prepared to undergo any more procedures. I eventually receive the biopsy results. Negative for H-Pylori .All those antibiotics had been unnecessary!

The pain in my pelvic region has increased tenfold and I still need to pee a lot. I return to my GP. She does a dip stick urinalysis. All clear, but gives me 3 days antibiotics "just in case". I don't get better, return again, see another doctor, yet another urinalysis, nothing shows up on the dip stick but she sends this one off to lab. She also performs and internal exam. Tells me there's a slight prolapse, nothing to concern her; well it's concerning me !

The doctor says I need to see a specialist, can't make up her mind, a gynaecologist or urologist, is she asking me? I'm given another short course of antibiotics; different ones....my symptoms go this time...for a week. I return to the my original GP, "nothing grew in the lab", I now feel like a fraud, a nutty menopausal crone, however GP says should see a specialist, a urologist ASAP & mentions this condition IC cystitis. What's that? Advised the NHS list is long, so can I afford private. I don't have insurance but I will pay anything, I'm in so much pain & discomfort. I feel like I'm in a living hell. My family are suffering as well. I'm being a complete bitch. Spending days in bed, curled up in ball crying. She gives me more antibiotics as they are helping somewhat. Tells me diazepam may also help so take that regularly alongside the other pain medication. She also sends me for complete abdominal ultrasound scans, nothing shows up. I'm really worried now, so also pay privately for an ovarian scan and blood test.. I'm really scared. Private ovarian scan is expensive but shows no abnormalities. I'm seen by a private urologist who carries out further urinalysis, ultrasound scans of bladder and kidneys. I decline a cystoscopy. I've researched this procedure and read this causes further damage. He's not at all happy with my decision, says only takes a couple of minutes. I still have horrible memories of the endoscopy a couple of months previous.

I also find out about Professor Malone-Lee and his research and treatment. I request a referral.

My GP continues to treat me with various antibiotics, (some make me unwell) I'm seen by Professor Malone-Lee who find pus cells in my fresh urine sample and tells me I don't have IC cystitis, I have OBBI.(hidden infection) I'm being listened too, he believes me, I'm not going mad and HE can help me. He tells me it won't be a quick fix but I'm not worried. I feel relief, like a big warm blanket has been wrapped round me, I feel safe. The professor changes my treatment and I begin feel better. The professor's team have seen something in my urine, that's a first. I'd been made to feel like a time waster by my local A&E, despite me being in so much pain I couldn't hardly stand on my own two feet, my GP surgery made me feel like I was wasting their time and I'm not being told I have to have painful procedures. I feel like I'm being cared for, I feel like a human being for the first time in a long time. Absolutely no issues contacting the

professor if I have any questions. Easier to contact him than it is to get an appointment with my own GP. All going well, I'm able to get on with my life again. Go on holidays, enjoy myself, how dare I! I return to my urologist for another routine appointment, he now informs he believes I have an infection within my bladder wall, he saw a little blood and pus cells in my last urinalysis. He tells me this condition requires treatment with long-term antibiotics he has no knowledge of the antibiotics required and that I should continue with my treatment from Professor Malone-Lee for this, however he is still happy to perform the cystoscopy for me !!!!!!.

Patient Impact Statement

I have had issues with my bladder for the past ten years. When I first started having abdominal pain, I had **numerous hospital tests and saw various consultants i.e. urologists and gynaecologists**. I was also hospitalised with severe kidney pain and UTI. Luckily during one of my hospitalisations one of the ward team suggested I be referred to Professor Malone-Lee. I have undergone invasive tests, such as flexible cystoscopy etc., but the other specialists were unable to offer any solutions to the pain and the UTIs. Once it had been ruled out that there were no surgical options to treat my issues, then the various specialists announced there was **nothing they could offer to help**. Professor Malone-Lee identified an infection through his urine microscopy test and was confident that this is something that could be dealt with.

When my infection is at its worst then I am unable to work, leave the house as I need to be near a toilet at all times, in constant pain, nausea, am unable to eat, unable to sleep, have a brain-fog, extreme fatigue, panic attacks and depression. I have at times felt suicidal because I was so unwell.

The Professor and his team run an excellent, specialist service and due to their specialist urine testing are able to identify when my infection is starting to oscillate upwards – something that standard NHS testing is unable to do. They are experts in this condition and are able to advise on treatment adjustments that help me manage this condition.

On one occasion when the clinic was not open I had to go to my **GP** in the interim and they **did not know what to do to treat me**. You cannot expect GPs to be expert in everything and they have no idea about how to control an ongoing embedded infection. I have been offered pain-killers, anti-anxiety meds, sleeping meds and counselling.

Without the treatment and support I have received from the Professor and his team I would not still be in full-time work, be able to pay my mortgage and support my family. When my infection is at its worst I become extremely fatigued, have a brain fog that is scary to experience and am basically unable to have any kind of normal life. **Treatment by the LUTS service run by the Professor and his dedicated team has kept me sane and alive.**

My treatment is not yet complete and without access to the LUTS clinic I am terrified of returning to square 1 with no access to expert advice from someone that can actually offer an effective treatment.

Patient Impact Statement

In August 2000 without warning I suddenly got a sharp acute stabbing pain in the bladder/urethra and a feeling of intense pressure. I also had symptoms of frequency and of needing to pass water up to 38 times a day. The pain was unbearable and I had the feeling that I always needed to pass water as I had this pressure sensation in my bladder as if I was carrying a huge boulder inside it.

I went to my .GP who thought I had a urinary infection and prescribed 5 days of antibiotics which did nothing. I went back and over the course of 7 weeks I was prescribed a further 4 different antibiotics each 7 days worth. None worked and I still had the pain and other symptoms. Finally a urine sample was taken it came back negative and my .GP told me that he couldn't prescribe anything more as I didn't have any infection!

Yet I still was in acute unbearable pain and very frightened. I knew something was seriously wrong.

In January 2001 after more weeks of pain and no medication, my GP to referred me to a gynaecologist through my private health cover. The gynaecologist performed a laparoscopy. The results of this were clear although I picked up an 'infection' during my time in the hospital and the results of this was that after the operation I was unable to pass urine for 16 hours. I was in great pain and an attempt to pass a catheter in failed. Urine sample showed 'mixed growth of doubtful significance and some red and white blood cells-possible contamination'. Based on this the specialist told me I needed a cystoscopy and because I had no infection it must be something serious in my bladder.

I was referred to a urologist. It had been 7 months and I was in acute pain with pressure and frequency. I was sure this was an infection but the doctors and specialists said no as my urine sample was negative so I was refused antibiotics.

I had the cystoscopy done in **March 2001**. Before the procedure I told the specialist that under no circumstances should he perform any other procedure on me other than the cystoscopy which I had under general anesthetic. **Yet he also performed a urethral dilation and stretched my urethra against my wishes. The excruciating pain experienced afterwards was unbearable**. It was unnecessary and gave me more pain. He said it was because I had a short urethra! This was complete nonsense. Up until August 2000 I had not experienced a single issue with my bladder/urethra.

It took me approximately 4 weeks of crippling pain to recover from the cystoscopy. The result was I had a thickened bladder lining. That's it. From this I worked out that this means the bladder lining is inflammed. No explanation from the urologist to why. I have no infections he said!

The years passed. I lived with the pain and passing water up to 30 times a day. **I saw another urologist in 2004** but they wanted to do a cystoscopy. I refused. Over the years when the pain was at its worse I would be checked for infection yet my sample was negative so no antibiotics. My life changed and I lived with the pain, pressure and frequency. Some days were worse than others. The pain could have me on the floor in agony it was unbearable.

In January 2014 I could no longer live this way with the pain and after much research found Professor James Malone-Lee. 13 years after becoming ill with this condition. I had my first appointment with him late January. For the first time in 13 years I was talking to someone who understood and recognised my symptoms. He explained how the short term 7 day antibiotics would not have worked as they were low dose and for a very short period. He explained how infection can persist for many weeks in the bladder without obvious signs in the urine. It can even be a very low grade infection that can remain in place for several years. I was amazed by his knowledge and information. I cried with relief that I had finally found someone who understood what was wrong with me and was willing to do everything to make me better. The Professor put me on Cephalexin 1 .gm bid twice daily and Azithromycin 500mg twice a week. Just 3 weeks later all my symptoms vanished. I was in shock. I had 2 whole weeks of no symptoms at all. After 13 years of pain and suffering. After those 2 weeks the pain did return but not as intense as it had been before and the pressure was less. Over the course of that year I experienced 4 months of no symptoms at all and the other times I did experience some flares and worsening of pressure and frequency. When this occurred then the antibiotic was changed or a new one was layered in. My urine was tested by a process called a sediment culture. This is a much more efficient way to test urine and it showed I had an enterococcus. The test also showed what antibiotics I was sensitive too.

In January and February 2015 I started to suffer from frequency again but I wanted to see how it went. I continued on antibiotics as instructed doubled the dose as the pain was becoming more regular. This was because a new biofilm had taken the place of the old one. So in April 2015 the Professor put me on a new antibiotic called Pivmecillinamin 400mg bid twice daily. Within 2 weeks all my symptoms vanished. It killed the infection-the biofilm. On 23rd June I stopped the antibiotics. I'm on none now. I have no pain and no other symptoms! I'm aware that could change at any time but for the moment I'm pain free and that is all thanks to the care of Professor James Malone-Lee. By prescribing high strength high dose antibiotics my acute occult urinary tract infection I've had for the13 years has been been killed.

I've had the best 1 year and 7 months just gone out of a total of almost 15 years spent living with acute pain and frequency again and pressure. I've got my life back and the only person who can take credit for that is Professor James Malone-Lee.

I pray that he can share his methods with urologists UK wide because otherwise millions of women will continue to be given low dose antibiotics or no antibiotics because their urine test is negative when in fact they do have an infection and it should not be labelled something like 'interstitial cystitis' because it CAN be treated and it CAN go.

Patient Impact Statement

My problems began in 1988 when I had my first ever urine infection. I was unable to get a GP's appointment but was given a prescription for 5 days antibiotics. It didn't improve and I was in severe pain forcing out drops of burning urine from an inflamed bladder. I tried again but couldn't get an appointment and was given 7 days of the same antibiotic. There was no improvement. In desperation I went to A&E and at last a sample was taken. I was given 7 days of Ampicillin and the severe burning left me but I was left with an inflamed bladder. Urine samples at the hospital showed no infection but I was still in considerable pain. I was referred to a gynaecologist .He performed a laparoscopy but this didn't reveal anything. He did see some vaginal scar tissue which he thought might be due to using a too large diaphragm.

I was then referred to a Urologist. He asked me if my baby slept and what my relationship with my husband was like. He performed a cystoscopy and a Urethral stretch and said I had Urethral Syndrome. Following this my pain was worse.

Later I was referred to a different hospital and 3 further cystoscopies and a bladder biopsy were taken. The first said my bladder was fine, mast cells were seen on the second and by the third, the bladder was now showing 'classic signs of IC and a possible Hunner's ulcer'.

Future treatments included DMSO, Pentosan, Accupuncture, 30mg per day oral prednisolone for a year, self catheterising steroid instillations and Heparin instillations. None of these helped at all.

An excellent GP felt that I had urine infections that weren't showing up. She got me to rush to the Pathology lab with a sample when I felt it was particularly painful and E Coli was found. She prescribed 6 weeks Norfloxacin, the pain went completely and normal life was resumed. After 30 months I had a brief urine infection while abroad and the pain returned. We found it very hard to cope with this psychologically.

I was referred to a pain clinic where I was prescribed Amitryptline (helpful) and Gabapentin which didn't help.

I was now referred to a different hospital where I was offered much of the treatments that had failed previously. Then a new treatment was offered prophylactic antibiotics. Initially there was a response but then it tailed off and stopped helping. I was given Heparin instillations.

I spent a fortune on alternative treatments, acupuncture and allergy testing etc. I tried giving up alcohol for 3 years and many diets.

The pain can be dreadful. It changes over the weeks and can change several times in a day. It may be felt in the lower back and move to the perineum, the vulva can feel like it's on fire, 'electric shocks' can be felt in the vagina. Sometimes the pain in my groin feels like a stake has been hammered through. During the worse times when I have the symptoms of an infection and the pain flares it is very hard to cope with and I have had suicidal thoughts. Many holidays and special family occasions have been ruined for me. Very few people know of my pain. Who wants to hear about a pain that moves around the pelvis, is mild one day and agonising another.

The only time I felt that someone understood my pain was when I described it to Professor Malone-Lee and his colleagues. He found infections in my urine. Was concerned about the high white cell count that had shown up for 25 years but hadn't created any interest. I began the long term antibiotic treatment. Progress is slow, but there is progress and I feel optimistic and hopeful. Whereas I might have seen a Urologist every 6 months in the past now I have one that will reply to my concerns by e mail usually within 24 hours. I travel 200 miles to London to give a urine sample and then await my telephone consultation. Full documentation is provided for myself and my GP.

I have never been as well supported.

Patient Impact Statement

I first visited Professor Malone-Lee's clinic in 2008, at the age of 24 after 4 years of misdiagnoses and unsuccessful treatments for my bladder urgency and frequency symptoms. By the time I was referred by chance to the Professor's clinic at the Whittington I was wetting myself several times a day. As a result I was extremely anxious about being publicly embarrassed at my job, which involved regular travelling and socialising, and especially about social situations in unfamiliar places. I also found that few people took it seriously as a problem. When I told the Prof of my symptoms at our first appointment he said, wide-eyed, 'You must be miserable!' I felt as if he were the first person to have understood my predicament.

GPs were either perplexed about or dismissive of my symptoms. One GP visibly stifled laughter when I explained the problem. Another helplessly told me that she was confused because my urine tested negative for any infection and because I hadn't given birth to any children, so my pelvic floor muscles should have been strong. I went away from that appointment without any solution. I did have one helpful doctor at a hospital in Kent, but her prescription of Solifenacin Succinate only had positive effects for a limited time.

The work of the Professor and his staff has had an enormous positive impact on my quality of life. Once diagnosed, the combined treatment of Nitrofurantoin and Solifenacin brought my infection under control within a year and a half, and the worst symptoms abated. However what has been invaluable is the ongoing care and consultation that the Whittington has provided me with over the past 7 years. In putting me forward for relatively new treatments like botox bladder injections (which I have now had three times) the clinic staff have given timely, useful and compassionate advice. And when my infection flares up - which is at least twice a year, for a period of several months at a time - I have found the clinic extremely responsive and friendly in providing me with advice and prescriptions, in person, over the phone and by email.

It is a struggle to do justice to the impact of all of their work, save to say that if I had not been referred to the Whittington and received treatment I cannot imagine how worn down and unhappy my health would have made me. Being able to stop worrying about my health has meant that I am able to invest energy in my relationships and in building a career in policy and public affairs. Most importantly my treatment has enabled me to regain control over my body, which seemed impossible those years ago.

Patient Impact Statement

I have suffered with chronic and recurrent UTIs since the age of 18 and am now 40. During my mid **twenties (around 2002-2004**) the infections were more frequent and the associated pain worsened. I went back and forth to my GP countless times, sometimes more than once a week when the pain was very bad. They repeatedly tested my urine with a dipstick and told me I had no infection. Sometimes they would prescribe me a week's worth of antibiotics but often they would send me away with nothing. I never felt that they believed me when I repeatedly told them about my symptoms. I knew that I couldn't possibly be making up a pain with such specific and localised characteristics but I couldn't get anyone to believe me. Eventually I was given Amitriptyline to help the pain and also because I had become depressed as a result of the grinding and relentless physical symptoms.

In 2003 I referred myself to a private urologist in desperation. Again, the tests rarely showed an infection. I had a cystoscopy which didn't show anything remarkable and was given a bladder stretch (I had previously had both of these treatments on the NHS and they did not get me any further forward). I was treated with intermittent antibiotics and also given a device that was supposed to emit electrical impulses in to the bladder wall which was intended to help with pain. None of this did anything to help my symptoms. After several months the private urologist said there was nothing else he could do for me other than prescribe me an anti-depressant (Dothiapin) and refer me to a pain specialist. I had a very adverse psychological reaction to the Dothiapin and became clinically depressed. **I had an extended period of time off work in 2003 with depression**.

After being hospitalized for several days with a kidney infection in 2004 I was referred to an NHS urology department where I had to do a series of urodynamics tests. I was also given a scan and told that my bladder wall was slightly thicker than normal which may be causing overactive bladder and was given some medication for this. In the meantime I continued to be treated by GPs with short term antibiotics. **Eventually (I think it was around 2006), I was referred to Professor Malone-Lee**. I was treated with an outstanding level of care at his clinic. The sophistication of the clinic's testing facilities mean that infection is detected immediately and treated accordingly. Patients like me often have multiple infections at one time and because of the nature of the condition, have to be treated with higher doses of antibiotic over a prolonged period. I am prone to quite extreme fluctuations in infection which need early identification and treatment to be managed effectively. Whenever I had a flare in my symptoms I was brought in for a test within 48 hours and had my medication assessed. Above all, Professor Malone-Lee and his staff have never doubted or questioned my symptoms and have always taken my condition very seriously. The nature of the condition means that I will always have ebbs and flows in levels of infection and associated symptoms, but the physical and mental relief that the Professor and his clinic have given me over the years is difficult to put in to words.

I am suffering from a flare in my symptoms at the moment and called my GP surgery last Monday morning for advice. The triage doctor I spoke to referred to my last notes from Professor Malone-Lee and was unsure how to treat me. I suggested that I revert to a previous combination of antibiotic, **which she agreed to so I have effectively had to treat myself. I have no professional medical knowledge and should not be making decisions about my medication**. I was also told to go to the surgery to provide a sample for analysis which came back negative.

I am very frightened about what the future holds for me both in terms of my physical but also my mental health.

Patient Impact Statement

I first developed a urine infection in June 2014, having one had one once before when I was much younger. I was treated by my GP with a short course of antibiotics, which were effective for a few days before the infection came back quite strongly. I went back to the GP and was told it was another infection, and was given another course of antibiotics; the same thing happened. My symptoms gradually became more persistent and more difficult, and this pattern repeated every couple of weeks; each time I had antibiotics for a week they seemed to become much worse afterwards. By November I was visiting the GP almost weekly with symptoms, pain and was becoming very depressed.

I suffered from severe pain in my urethra, pain in my abdomen and higher legs, lack of sleep (due to pain and needing to get up and use the toilet between 2 and 8 times per night), needing to urinate at all times, rather than being relieved by actually going, and tight feelings in the urethra. I didn't feel that they GPs really knew what it was as they said different things and never seemed clear what infection it was. They told me sometimes that I had an infection, and others that it didn't show up with one, but also that the tests often do not show them when they are there.

In December 2014 I was seen in a urology department where I was given a prophylactic antibiotic (low dose). I took this for a period of two months and found no change. During this time the symptoms became almost permanent, rather than going up and down every few days. I was referred for a cystoscopy, which was extremely traumatic due to being infected at the time. Following this, my symptoms were terrible, worse than they had been and became constant. I was unable to sit down comfortably for three weeks. I was then told that I had overactive bladder and given medication for this. A month later another specialist told me I didn't have overactive bladder and put me back on lose dose antibiotics.

Finally, I heard about the LUTS clinic. I was seen quickly in April, and treated better than in any medical situation I have ever been in. I cried during my first appointment with relief to be listened to. I left the appointment with a diagnosis of a chronic bacterial infection, and a clear plan of how to treat it. I was monitored carefully to make sure that I was on the best antibiotic for me, and when I flared the Professor would consider and alter medication if necessary. Each time his advice created an improvement in my symptoms. My symptoms gradually started to improve and I was able to sleep through the night and go out without being in pain more often. Although I still had flares they became less persistent and less often. The stress of the condition on my marriage lessened because I felt supported and well treated.

My symptoms lowered until I fell pregnant 12 weeks ago. They then flared considerably which is common in pregnancy. The Professor was very careful about what to do given my pregnancy and arranged to monitor me monthly, due to the risk of miscarriage associated with increased white blood cells and infection (as I had had before his treatment). Now that the clinic is closed, I have no-one to monitor my white blood cells and infection cells. This means I would not necessarily know if the white cells increased, and therefore if my pregnancy became at risk. I lowered the dosage the week before last, worried that I might not be able to access further medication as needed. Two days later I suffered severe pain, and a huge flare that lasted for over a week. I felt very stressed and anxious about the risk to the pregnancy of letting the infection run riot. I have since returned to the dose given by Professor, and my symptoms are now becoming under control again. I believe that the decision to close the clinic leaves me with the risk of further bladder and urethral damage, further anxiety and depression, and significant risks to my pregnancy. It is a well-known fact that urine infections in pregnancy and can be complicated and dangerous if they are not treated adequately.

Patient Impact Statement

My bladder problems started after I was catheterised for five weeks following a partial bladder resection to remove a nodule of endometriosis. Unbeknown to me, this was going to be the cause of my 2.5 year battle with an embedded bladder infection, undetectable by standard NHS urine testing. The bladder pain was slow to progress in the beginning, but over a month it became unbearable and I was in daily pain with frequency. During this month I had submitted various urine samples to my GP but the standard NHS testing kept coming back as negative. This completely messed with my head because I was certain I had a bladder infection. As a last resort I attended A&E in the hope of help, but all I was offered was codeine and sent on my way. They did however, test my urine at the hospital, and subsequently it showed up positive but with 'contamination'. This seems to be the interpretation for a urine sample that shows up multiple bugs. So I was prescribed the usual short course of antibiotics, which helped 80% but then as soon as I finished the course, my symptoms returned full force. Over the course of a few months I was trialled on many different antibiotics by my GP in the hope that it would help, but as soon as I stopped taking the antibiotics, the same thing would happen…my symptoms returned. I had to stop work because I was unfit to function. I was incredibly anxious and depressed because no doctor was able to find what was wrong with me. I could not socialise or have a normal sex life because of the pain. I lost a lot of weight because of how anxious and depressed I was.

My GP had no other option but to refer me to a urologist on the NHS. This experience turned out to be absolutely hopeless! The urologist put a camera in my bladder and because nothing was visible **he simply told me it was all in my head and down to the stress "of trying for a baby!"** The procedure was very painful and traumatic!

Left on my own in severe daily pain, I became suicidal. I tried numerous other therapies and remedies such as acupuncture, d-mannose, changing my diet, etc. but nothing worked. My GP trialled me on various different painkillers, such as co-dydramol, gabapentin, pregabalin, codeine, and amitriptyline. Nothing took the edge off. I was categorised by my GP and urologist as having '**Painful Bladder Syndrome' or 'Interstitial Cystitis'! What a load of rubbish these diagnoses are!**

It was only when I was desperately searching for a cure online that I came across a forum mentioning Professor James Malone-Lee. My GP very helpfully referred me to Professor Lee on the NHS and following having the Professor's more precise urine testing, 2 main pathogens – e-coli and enterococcus, showed up on my results. I was SO relieved to finally have an infection confirmed, and I felt like I wasn't going crazy after all! He assured me that he would not give up on me, and that we would get a hold of this infection, but that it would take 'dogged persistence' and the trialling of different combinations of antibiotics for possibly quite some time. I appreciated his honesty and was so happy to FINALLY have a proper diagnosis and a treatment plan. This automatically helped with my anxiety and depression. I felt that there was light at the end of the tunnel.

Once I started on the antibiotics, along with the amitriptyline that I had continued to take, my pain started to subside. Over the course of the last 2 years with the Professor, I have been incredibly well looked after! He and his team have been a godsend to me! Gradually over time my white blood cells and epithelial cells have fluctuated, but are on the decline. I have had very few flare ups, and each time I have, the Professor has adjusted my antibiotics and the flare has been taken under control again. The amitriptyline had no effect without the antibiotics, but together, I am pain and frequency free 95% of the time. I can live my life again, go to work, socialise, exercise, make love, and most importantly – I am now pregnant! No other doctor would have touched me with a 10ft bargepole with me being pregnant and diagnosed with an infection….but the Professor has. He has kept a very close eye on my pregnancy with more frequent checkups and provided me with pregnancy friendly antibiotics. He has been my saviour and for that I am eternally grateful to him and his wonderful team! I am only on one antibiotic at present and I hope that within another year or less, I can come off the antibiotics completely. I would also like to mention that, at no point under the care of Professor Lee have I contracted C-Diff. I have had hardly any side effects, and if I did, then the Professor would straight away adjust the medication regime.

I just hope that all the women who are suffering like I did, with inefficient standard NHS urine tests and incompetent urologists, can come across the same information that I did on the Internet and seek help from the only doctor in the UK who actually knows what he's talking about!.....Professor James Malone-Lee."

Patient Impact Statement

I had never suffered with UTIs before becoming **unwell in 2008**. I had no bladder problems or pain and had no experience AT ALL of 'bladder issues'. I was independent, working full time, exercising and living a full life. Following what I was told were' routine' pelvic investigations, for some abdominal pressure gynaecological bleeding, which included a cystoscopy, I had the most severe urethral pain, bladder pain and symptoms. I had contracted an infection.. I was given a short course of interim antibiotics which did not help. The urine sample was lost and I had to do repeat. After another short course, I had no relief from the agonising pain and discomfort I was in. I visited another GP, who said there was no infection now showing and I should see a Urologis., I think because I had never had a UTI before, I accepted what I was told and thought I must have Interstitial Cystitis or damage from the procedures. I visited various Urologists, Urogynaecologists and had scans and further tests. I was offered more procedures but declined as I did not want to undergo further invasive investigations when that was precisely what had started it off to start with. No one seemed to have any idea what was wrong or what could have happened. This in itself was distressing and very frightening. I experienced very low mood and fear and anxiety as I did not know what had happened to me.

From 2008 to 2014 I became more and more unwell and suffered constant severe urethral and bladder pain which spread into my pelvic floor as well, constant irritation, burning, frequency, urgency, incontinence and cyclical worsening of my symptoms. I tried many, many treatments: physical therapy, OAB meds, nerve treatments, PTNS, acupuncture and had scans and many consultations. I tried a variety of medications as well such as short term antibiotics, OAB medication, nerve pain treatments, SSRIs, and hormonal therapies. I tried 'integrative' treatments too spending thousands in trying to free myself from the never ending pain. From the day this happened to me I was unable to sleep through the night due to severe bladder pain and symptoms and I also became more and more systemically unwell**. I lost my career and subsequently lost another job I tried to take instead. I** have suffered more than I can describe here but to be in pain for years on end with no relief, no diagnosis, and no help is beyond endurable.

I was told that I should learn to live with this pain and that there was no hope for improvements. At one specialist pain clinic I came out feeling suicidal and had to call a close friend to come and get me home as I was so distressed by their uncaring and cold attitude. They seemed amazed that I still wanted to find out what had happened to me and whether there was hope for improvement. I have been told that they only 'manage' pain if you have been experiencing it for more than 3 months and do not look to treat. At various times I visited Consultants and GP's telling them I felt I had an infection – they just dismissed me saying I was having a 'flare' of pain. **I had raised levels of white blood cells at various times but was told it meant nothing by different doctors and clinics**. I also had many specialists describe my problems as 'irritable bladder' - I realised these doctors had absolutely no concept of the level of my pain and the extent of my suffering. This is a severely painful, depressing and debilitating condition. **I saw Urologists, Gynaecologists, Pelvic Pain specialists, Neurologists, Pelvic Floor Specialists - around ten Consultants overall**. I spent thousands on private treatments and appointments. I changed my diet and have drunk only water for seven years. I knew I could not live the rest of my life with this pain – every day activities such as sleeping, walking or even travelling were impossible and relentlessly painful and yet there was no diagnosis , no explanation and no hope for improvement.

After 11 months with Professor Malone Lee I have significant pain reduction and notable improvements in my other pelvic symptoms. I felt reassured by the Professor's attentive and empathetic manner and his total focus on recovery as well as his logical approach to my history and the abrupt onset of my symptoms

from surgery. He told me he believed I have had an infection for the last 7 years since the time of the surgeries and the equipment/hospital based infection. He diagnosed me with a chronic, embedded infection using better validated diagnostic tools than those widely available on the NHS. His diagnosis and treatment were correct - every month that I have treated with him I have improved and the pain has lessened. My severe depression and anxiety has lifted and for the first time I have begun to hope of returning to work and living something like a 'normal' life. I have finally got a diagnosis and a treatment plan. Professor Malone Lee is an exceptional doctor, expressing sadness and compassion for my needless suffering and gave me every hope that I could slowly recover from this. He was organized, efficient, and caring and this has been my experience of his clinic and all of his team. I have been monitored closely and with a much greater level of availability than any doctor I have ever consulted with.

It is hard to put into words my gratitude for the work that the Professor and his team are doing, and I personally have given the details to two other women who are similarly suffering and have been dismissed time and time again. I do not know what might have happened to me had I not found the Professor and I do not know what will happen to me should this vital, life saving treatment be withdrawn.

Patient Impact Statement

My infection started in **August 2012** after a swim in the ocean. The urine culture taken revealed two bacteria **ENTERECOCCUS FAECALIS (10^6)** and **COLI (10^5)**. I had extreme frequency and pressure making me go to the toilet every 15 minutes and even then not feeling relief. The feeling of not being fully empty stayed with me at all times. As the culture showed significant counts of bacteria, I was put on the course of antibiotics but it was never longer than 2 weeks. My symptoms lessened a little bit but they never vanished. Since there was also ureoplasma discovered in my urine, antibiotics were changed every month. This time the courses were longer, lasting a month and then they were changed. However, I did not feel any relief as the symptoms remained pretty the same.

When I discovered Professor James Malone-Lee after coming a long way from Poland as an international patient, I knew that ureoplasma was not responsible for the way I felt but enterecoccus faecalis and coli. These were the bacteria that buried deep into the bladder tissues and surrounded themselves with biofilm making them totally insusceptible to antibiotics. Targeting antibiotics at them was like chipping away at a rock with a feather. That explains why long-term high dose antibiotics are needed and that the immediate reaction does not come straight away due to the existence of biofilm and the resistance factor. It is highly possible that one bacteria may be killed off but another occupies the vacated place, accounting for the deterioration in symptoms. The Professor treats based on symptoms as well as urine culture results whereas the previous doctors especially urologists dismiss the patient for the mere reason the tests do not show up any bacteria even though there are acute symptoms. They do not also believe in biofilm, thus disregarding the treatment with long-term antibiotics whereas it is so helpful for many patients. Urologists prescribe invasive procedures like urodynamics and cystoscopy whereas they may only introduce new bacteria into the already existing mix and in fact do not offer answers regarding the present infection. I have seen lots of urologists like that and they have not been very helpful and understanding.

I am so happy I have found the professor who does not give up on any patient even if the case seems to be unresolvable and hopeless. Since it is a long-term process and one antibiotic does not resolve the complex issue of infection, I am not cured yet but I know for sure that the professor is right believing in biofilm, treating not only based on urine results but also symptoms and prescribing long-term antibiotics. I am so lucky I have come across his clinic and I truly believe he cures and saves lots of people suffering from this terrible affliction.

In view of all **this I plead you fervently to reinstate Professor James Malone-Lee and his clinic** as without him, his dedication and research thousands of lives will simply be marred by pain, uncured chronic infection and lots of people who have already achieved brilliant results with the treatment may go back to square on. The method of Professor is the only viable method right now to tackle the long-term chronic infection and the biofilm which the bacteria are entangled in until the new, promising treatment arrives.

Patient Impact Statement

I contracted a UTI in the middle of October 2013. I was 42. I am a fit and active person who takes regular exercise, eats a balanced and healthy diet, doesn't smoke and drinks to moderation. I had not had any problems with my urinary tract before prior to this infection. In fact, I have always been extremely healthy. I went to my GP who took a urine sample which was analysed at my local hospital (Frimley Park) E-Coli was discovered and I was treated initially with nitrofurantoin. I think this was a 5 day course of 3 tablets a day. Initially I felt better but after 3/4 days I felt my discomfort return.
My symptoms were as follows:

malaise, tiredness, weakness and all over body aching, Cold like symptoms, sharp aching on my left side, aching in my kidney area on the left side, bladder cramping, period pain type cramps, a feeling of crawling and scraping in the bladder and urethra

There was no frequency or sensation of burning as one would experience with a classic case of cystitis
At its worst I would have pain in my ribs, pain in my hip and legs and all around the pelvic area, weakness in my hip and thigh

My GP and was given 2 further courses of antibiotics - this time co-amoxyclav. Again - there was an initial improvement and a return to the discomfort. Mainly kidney pain and back ache but also the crawling bladder sensation. Further urine tests were coming back as clear and my GP was at a loss as to explain the problem. In December 2013, I was sent for a renal ultrasound. This was deemed normal. I also had blood tests for kidney function, inflammatory markers and also tests for problems with my ovaries which may indicate cancer. All came back as normal. Over Christmas that year I felt back to normal. But by January 2014 all the symptoms had returned. I researched and found the term 'Interstitial Cystitis'. I became a member of the Cystitis and Over-active Bladder Foundation (COB) and followed their advice on eating certain foods, and keeping my diet bland and acid free. This had no effect whatsoever! I took herbal remedies and cranberry tablets having spent a fortune. All to no avail. Next my GP referred me to have a CT scan. This came back as normal. Further urine tests came back clear showing no infection. But still the symptoms remained and I was becoming very despondent indeed. My GP prescribed amitriptyline (this did not work for the pain) and then referred me to a urologist.

By this time, after 8 months or so of pain and dead ends my mental health began to suffer. I was taking propranolol for anxiety and was struggling to maintain a positive outlook, look after my two sons as a single parent and also teach my class of children in my job as an infant teacher. Having this condition is all consuming. You cannot take a pain killer and carry on... It was utterly draining. At this time, May 2014, I was told, via the COB Foundation of the work of Professor James Malone-Lee. Other women who had similar problems to me had reported success with his treatment. I was able to get in contact with these women via COB and get the details of the Professor's clinic. Within MINUTES of conducting a urine test he was able to say that I did have an infection that had not been cleared. I almost cried with relief that at last somebody could tell me what was wrong with me. He set me off on a course of antibiotics gave me lots of paperwork explaining his treatment regime and research protocol. I took this information to my GP couldn't understand why I was on antibiotics when all my urine tests with the NHS were clear! He was sceptical about long term antibiotic use and the fact this was a private appointment and was not willing to refer me to the Professor as an NHS patient. There was a distinct lack of willingness to even look into the work the Professor is doing and to consider that it may have some important results for women suffering as I was. I was also told to 'reduce my stress'. This was incredibly frustrating. My condition was causing the stress. Not the other way round!

Sadly, the appointment with the urologist was the same. I took the paperwork to him to explain the Professor's findings. He didn't read it He stated that I was 'barren' for signs of infection and there was nothing wrong with my urinary tract. He claimed that instead I was stressed and had IBS and should look at changing my diet. He asked me to point to areas on my body to describe where the pain was. He said 'How do you know that's your bladder? How do you know that it is your kidney that's painful?'. He completely

refused to consider that I am aware of parts of my body and having lived with pain for 9 months did have a good idea of what was hurting and where. In short, he refused to listen to anything I had to say.Despite him declaring there was no problem with my urinary tract, he decided I should have a cystoscopy to investigate what might be going on. It would be under general anaesthetic because 'it will hurt'. I left the appointment in shock and disbelief. Needless to say I refused to continue with his treatment plan.

Instead I continued with Professor Malone-Lee's treatment and despite some ups and downs and changes to the antibiotic regime, by May 2015 I was feeling a lot better and in control of my symptoms. The regular urine tests that the professor conducted showed on graphs that that my infection declined over time and was almost at zero. My quality of life and mental health improved immeasurably.
There have been ups and downs and an increase in symptoms and the professor assured me he would get me totally well and off antibiotics. I was due to see him on 27th October to adjust my medicine and to test my urine to sort out this current flare. The fact my access to this appointment was stopped has meant my discomfort has increased and I am increasingly anxious about my symptoms worsening without access to the Professor's care. I dread to think what will happen once my medicine runs out. There has been no-one else who I have seen with the knowledge and expertise to sort out my problem. I live in fear and high anxiety as to what will happen next. I do not feel that a return to appointments provided for me by other specialists will help me. As the above account illustrates, all the specialists I saw and the tests I had, failed to find any problem. Only the Professor was able to ascertain this. It is his treatment that has improved my condition and I feel is the only way forward for me.

Patient Impact Statement

I had what seemed to be a straightforward UTI in September 2013. I went to the GP, blood and white blood cells were present so I was prescribed 3 days of antibiotics. This seemed to work, however 3 days later I felt the same symptoms.

I went back to the GP, this time my urine was cultured but there were no bacteria present. White blood cell count remained high, so I was prescribed another 3 days of antibiotics. This repeated itself about 4 or 5 times. I was then referred to a urologist by my GP who had no idea what else to do with me.

The urologist sent me for about 5 different scans (including CT, ultrasound and CAT) and urodynamic testing. None of these showed up any abnormality. I also had 3 more urine tests at intervals of about 3 weeks. Every time my white blood cell count was high, although the urologist dismissed this and said that I must have had another acute infection each time (I hadn't).

In the end, the urologist referred me back to my GP as he didn't know what was going on. He suggested that I had had a kidney infection and my body was just 'slow at recovering' although I wasn't recovering at all.

I was feeling flu like with terrible pain in my left flank, punctuated with incredibly painful bladder symptoms intermittently. I continued to work full time (I had just started my first graduate job) as I didn't feel confident to take time off. I ended up fainting in a team meeting and being taken to A and E. I was admitted even though bacteria did not present in my urine as my inflammatory markers and temperature were elevated enough for the doctors to treat a kidney infection. **I spent 2 nights in the Royal London and was given IV gentamicin.**

Over the next 3 months I was admitted twice more and given the same treatment each time. My symptoms improved slightly**, but as soon as the treatment stopped, I would deteriorate again very quickly**. I was even sent home with a cannula **in my hand and a nurse came round every morning to administer IV antibiotics for a week**. Again, some improvement but very quickly went downhill after the treatment was stopped.

Throughout this time (about 6 months in total) I felt very alone and unsupported by the medical community. No one had answers, and no one seemed very interested to try and help. I was continually passed on to new doctors to become someone else's responsibility.

It was in February of 2014 that quite by chance, my mother spoke to a friend about my illness and the Professor was suggested. I had little hope that anything would be different as I felt I had tried it all and heard it all before. However, after **my first appointment with the Professor I knew I had found the person who would get me well again**. He was describing all my symptoms to me before I had opened my mouth following a urinalysis done there and then at my appointment.

Since I have started following the Professor's regime, I have made slow but steady progress. By Christmas 2014 I was leading a relatively normal life again, and even sleeping through the night!

When the news about the clinic's suspension was released, I was due to have an appointment with the Professor the next day. This was to discuss the results of my latest urinalysis which Professor was not happy with. I had been feeling slightly worse leading to this appointment so to have poor results was no surprise. He wanted to alter my current antibiotic regime (which he has done 3 or 4 times since the start of treatment) and each time I would feel a marked change in my symptoms. Now, almost 2 weeks after I was due to change my antibiotics, I am feeling much worse. The flank pain is now severe; I have a burning bladder, and feel flu-like.

Without the Professor's care and expertise I worry that I will go back to square one, and I will again be in and out of hospital receiving partial treatment and being passed around between specialists.

To stop treatment which has been so effective, and for me totally side-effect free, seems totally negligent. The Professor did send me for blood tests to prove that I was without any side effects after 12 months of treatment. All tests came back normal.

I have received no alternative clinical advice since the suspension of the clinic, despite having contacting the hospital and the new Helpline numerous times. This is all while my condition deteriorates with no solution presented.

Patient Impact Statement

I have had one or two urinary tract infections ("UTIs") per annum since my early 20s (I am now 34), which would usually respond to a short course of trimethoprim. My nightmare began after giving birth to my daughter in April 2013: I had a horrendous experience and ended up with, *inter alia*, recto- and ano-vaginal fistulas, which whilst corrected with surgery, have left me battling a chronic UTI.

Treatment prior to Professor James Malone-Lee (the "Professor"):

I saw numerous consultants throughout the period from immediately post-labour (April 2013) to being referred to the Professor (June 2014). Throughout this period I was on near constant short-term antibiotic courses, including (but not exhaustively) co-amoixclav, trimethoprim, cefalexin, nitrofurantoin (extremely high doses of this for a few months), and even metronidazole which left me feeling extremely mentally confused, weak and very ill. Throughout this time I was passing blood, was exhausted, had horrendous burning of the vagina, frequent need to urinate, and was mentally and physically unable to cope and reliant upon my parents to help me to care for my baby.

The consultants all had conflicting advice in relation to UTIs, and it is now clear that they were not equipped to deal with a chronic UTI, which is a very different beast. The only common advice that I received was to take a conventional UTI test to establish that there really is an infection and the antibiotic best suited for it. I regularly failed the conventional UTI tests, and was met by patronising consultants, who seemed to want to believe that my symptoms were psychosomatic, despite my genuine pain and illness.

The last UTI test did manage to identify one huge growth of enterococcus, and led to my referral to the Professor: by this point, having researched enterococcus on the internet - feeling unable to trust the consultants' advice, given my worsening condition - I was terrified that I wouldn't live to see my daughter grow up.

Treatment with the Professor:

Upon meeting the professor, I felt instant relief. He reassured me that his patients regularly fail conventional UTI tests. Furthermore, he identified not one, but a couple of bacterial strains, and recommended an oral antiseptic in conjunction with a broad-spectrum antibiotic, which had an incredible impact on the infection. I cried from happiness when I saw my graph results.

His novel way of testing my urine sample under a microscope was, and still is, amazing: I suffer from ovarian cysts and candida, and at times it is difficult to discern UTI symptoms from other causes, so I rely single-handedly upon the Professor's tests and his diagnosis and prescription. For the first time since my daughter, I knew instinctively that I could trust a consultant: he was caring and extremely knowledgeable on the subject.

In January, I managed to stop the antibiotics altogether. The Professor forewarned me that the infection may well oscillate, as I was stopping the medication early as my candida was flaring up. It took several months before the infection returned and I am under the Professor's care again, as I failed to spot the early symptoms quickly (due to an ovarian cyst), and so delayed resuming antibiotics which would have stopped it. I have full faith that with his help, I can be cured of my chronic UTI and put my ordeal behind me.

Patient Impact Statement

My mother is 90 and lives in a care home. She has dementia and my sister and I have Power of Attorney over her affairs. I have accompanied my mother to all her appointments at the LUTS clinic, when it was in Archway and when it moved to Hornsey.

She was referred to the LUTS clinic because of persistent and very troubling urinary incontinence. Her first appointment was 9/6/11 and Professor Malone-Lee diagnosed her with an overactive bladder caused by chronic urine infection. Since then she has had regular treatment for what has proved to be a very recalcitrant infection. Throughout this time she has been monitored very carefully and treated with great respect and care by the Professor and his team. Her last appointment was 18/9/15 and she was due to have an appointment today, which obviously did not take place due to the suspension of the clinic.

If her treatment (according to the Professor's protocols) is stopped, she is going to become very ill very quickly. This could be prevented according to the Professor's treatment methods.

Patient Impact Statement

I have been a patient of Professor Malone-Lee since last summer. I was referred to him following previous treatment by

a) a consultant gynaecologist
b) a consultant uro-gynaecologist
c) a consultant urologist

I started to suffer from lower urinary tract symptoms in 2007 after a full hysterectomy. These three clinicians each had a different view of what was causing my symptoms. **Not one of them** thought that my urinary problems were due to an infection. They recommended invasive tests, invasive procedures and drug treatment (not antibiotics) I felt desperate as my urinary /continence problems were affecting everyday life.

Professor Malone-Lee and his team diagnosed a chronic UTI and started antibiotic treatment. I have experienced an improvement in my symptoms.

At the beginning of this year I was given a confirmed diagnosis of relapsing/remitting multiple sclerosis, I am treated by the Neurology team at Charring Cross Hospital. One of the many symptoms of MS (especially so in my case) is a bladder problem. My treatment - using the Professor's protocols is helping to control this. I am very worried when I think about what the future holds for me bladder-wise without this successful treatment.

Patient Impact Statement

Summary of problem (summer 2015)

16 UTIs in the last year.

Symptoms of inflamed bladder between acute episodes of infection.

25-year-old female almost **completely sexually abstinent** to avoid urinary infections.

Sex very painful. Anterior vaginal pain reflects urethral and bladder inflammation.

Prior to Prof. Malone-Lee I felt extremely hopeless for my future. I **started to believe that I would not be able to cope with the demanding profession I had chosen. I was terrified that I would never have a fulfilling romantic relationship**.

Treatments and investigations for recurrent urinary tract infections

(1) GPs:

Treated mainly by GPs in NHS walk-ins, mostly at night. Never able to wait for a routine appointment during acute UTI.

Acute UTI: dipstick always positive, and symptom resolution always occurred with appropriate antibiotics. When antibiotics were delayed, symptoms worsened until appropriate antibiotics given.

NHS walk-ins do not send urine cultures. Whenever GP was available to send cultures, antibiotics had already been started.

2009: urine culture grew **multi-drug resistant *Staphylococcus saprophyticus.***

2014: asked by a walk-in GP to compare the size of my partners' genitals in relation to my symptoms, which I did not feel was appropriate or relevant. He emphasized that my UTIs probably happen because I am "scrubbing" my vagina. I said I had received plenty of reasonable hygiene advice already and was not "scrubbing". He also informed me that any ultrasounds or cultures would probably NOT provide a diagnosis, and that I would find no solution **unless I changed my sexual practices.** I pointed out **that I could not have real 'sexual practices' i**n the first place. 2015: **I deteriorated** with daily symptoms of overactive bladder and pain. GP was perplexed. She prescribed daily cephalexin 120mg, with no improvement after several months.

(2) Urogynecologist:

In April 2015 consulted with a private urogynecologist. She trained with Prof. Malone-Lee in the past. She was very soothing and understanding of my suffering.

Initial urine grew **multi-drug resistant *E. coli.*** After a week's course of antibiotics, further urine cultures grew **multi-drug resistant *Klebsiella pneumoniae.***

Started on 3-month "cycling" regime: Doxycycline, Nitrofurantoin and Trimethoprim, each taken for 1 month.

I developed several acute UTIs during treatment. Any cultures taken during this treatment were negative.

The chronic overactive bladder symptoms had not resolved either. I was **struggling to revise** for my exams as I was in constant pain, and **unable to sleep** due to severe nocturia.

My urogynecologist supported me by referring to Professor Malone-Lee for his opinion.

(3) Professor Malone-Lee:

In August 2015, I was referred to Professor Malone-Lee as a private patient.

Prof. himself examined my urine sample (fresh, unspun, unstained) immediately. He examined the culture and renal ultrasound reports provided by my urogynecologist.

In our consultation, I was informed that I have a "barn-door" chronic urinary infection. **It was very comforting to hear that this could definitely be treated.** He educated me with extensive reading material with advice and summaries of his research.

I was reassured that I could contact him via email and **receive a response within 24 hours**. This was a bailout plan in case of side effects or acute flares. **I have never felt so well looked after.**

Initial treatment was Cephalexin 1g twice daily + Methanamine Hippurate (Hipprex):

- I developed a “flare” after two weeks. I remained patient for 2 more weeks, after which Cephalexin was increased to 1g 3x daily, and then after a week to 1g 4x daily.
- **Success!!** Symptom-free at last. I could have sex, which was relatively painless with no acute flare afterwards. This was the first time this has ever happened **in my life.**
- Reduced Cephalexin to 1g 2x daily after acute flare resolved**. This was a mistake**. Symptoms returned immediately with vengeance.
- The dose of Cephalexin was increased to 1g 4x daily. We waited over a week, but I **became so ill I could not attend** my university placements.
- Layered in Azithromycin 500mg daily, for three days, and thrice weekly thereafter**.** No improvement so escalated to Azithromycin 500mg daily. Massive improvement! Prof told me to see him soon.

However, Professor Malone-Lee was suspended from seeing patients before I could consult with him regarding this recent dose change.

I have been taking Azithromycin daily as per his advice, and my symptoms have **almost resolved!!** My regimen could be perfected further, and I am anxious that I cannot consult with Prof. **I am terrified of what could happen to me if my treatment is suddenly discontinued.**

Patient Impact Statement

I was 22 when I had my first UTI. Because it was the weekend I had to go to A&E. Being tested positive from a quick urine test, I was given a week's dosage of Trimethoprim, as it 'worked for most women'. A week later I was still unwell and went to my GP. My GP was reluctant to give me another antibiotic, stating that the antibiotic must have worked. However she still sent a urine sample and a week later we discovered that I had been on the wrong antibiotic. I was given a three day dosage of the right antibiotic. However I still felt unwell and felt that the dosage should have been for longer. I went straight back to the GP and she refused to treat me, saying that the antibiotics must have worked. I did a urine sample and the quick test indicated no sign of infection. Yet I still kept getting UTIs. I had never felt like this before and I wanted to get better. I kept waiting in waiting rooms for the next five months, being rejected with different responses. I remember at one point I went to the GP 6 times in 2 weeks. At many times the GP would look at the clock irritably. They would say that my symptoms were 'too vague' to diagnose, even though I felt the symptoms of a urine infection. They would keep suggesting that I had an STD, even though I kept telling them that I had been already tested a few times for this. They would tell me I felt this way as a result of 'constipation' - I never had had any difficulty with constipation. The GP would press against my stomach and say my bowel was full and therefore that the explanation behind why I still felt like I had a UTI. Between those months they would routinely give me a mere three day dosage of an antibiotic, often three weeks apart because it took so long to convince them to help me. Virtually every single time I was given antibiotics without any urine sample being sent to determine whether it was the right one. I felt as though I was going mad. I had never been ill before, and here I was being treated as though I was a nuisance and this foreign feeling made me feel awful. I kept sending off urine tests, mostly getting a 'mixed growth' result, which is indicative of an infection, but the GPs would infer this as a reason for no treatment. Sometimes the urine test would come back positive and they would once again treat me with a three day dosage. I kept coming in giving in urine samples, as if I was gambling and hoping that the next sample would show I was unwell but more often than not it came with a mixed growth and I was sent home untreated. After five months my mother convinced me to change GPS. At the new practcse I discovered that I should have been given a seven day dosage to treat a returning UTI. However even with this treatment I would still keep feeling as though I kept getting ill. I went to feeling as though I had a UTI once a week. I was given ciprofloxacin by a GP for a week and because of this antibiotic I still feel as though I have chronic joint pain to this day. Over the course of the past two years, I have gone from perfectly healthy to now feeling as though mutilated from the neglect of a few practitioners. I remember avidly arguing with a specialist before having a cystoscopy, stating that I most definitely still had an infection and therefore should not have the procedure. But it was his coldness and the situation that had left me with a sense of helplessness and I still underwent the procedure. Straight after this procedure I experienced vulvadinya (now cured) but the subsequent numbness I experienced in the clitoral and vulvar region has not really improved since. I now feel as though I have a constant, unwavering UTI. Professor Malone Lee was making me feel better – but now since his treatment has stopped altogether, I have relentless kidney pain and I feel as though I may not be able to support myself anymore.

Patient Impact Statement

My bladder success story – all down to Professor James Malone-Lee:

Three years ago I suddenly came down with what felt like very severe cystitis. I also had a temperature, and was very shaky and nauseous. I went to A&E as it felt too serious to wait. I was given a 3 day dose of antibiotics, which got rid of the pain on urination, but not the bladder pain and frequency. **I went to my GP who** tested for a UTI. She found no evidence of infection but gave me another 3 day dose of antibiotics. These appeared to make no difference, and my symptoms worsened rapidly. I was becoming scared and repeatedly went back to the GP who dismissed me because she could find no evidence of a UTI. I was prescribed bladder relaxants, but these didn't help at all. I was also given diazepam, especially to cope over the weekends, because I was starting to panic about the constant pain.

By now my symptoms were a lot worse - constant searing agonising bladder pain, a strange vibrating sensation in my bladder, pain again on urination, and a very strong urge to urinate all the time. I was also starting to shake uncontrollably at times – at times my body would convulse in pain, and I could feel a surge of adrenaline coursing through my body. By this time I had developed severe anxiety. I was unable to work, unable to sleep, unable to eat, and unable to look after my two children.

I was sent to a urologist who said that I may get better, but may not, or may have painful bladder syndrome, and that there was nothing he could do for me, but he did do tests to check that I didn't have bladder cancer and I had various scans and a tube inserted through my urethra into my bladder to check. Everything came back non remarkable. I went to see a different urologist privately. He also said that there was nothing he could do for me, but suggested various invasive procedures to check my bladder, repeating what had already been done on the NHS.

After a while, with no answers, I began to develop depression as well as the anxiety. I felt suicidal. My husband had to hide the knives in the house because I wanted to cut out my bladder myself at times, or kill myself because I was in so much pain and felt like I was being a neglectful mother to my children.

I was sent to a psychiatrist who said that I was "regressing into being a child" (!). This was my lowest point. But he did at least prescribe Lyrica and Duloxetine which took the edge off the pain. (These are anti-anxiety pills and anti-depressants that also help with nerve pain).

Finally, after 8 months, my urologist admitted he could do nothing further for me and referred me to the amazing Professor James Malone-Lee. What a difference! I thought that he would dismiss me like all the others, but he took the time to listen to all my symptoms (rather than the other urologists who, at times, had simply spoken to my husband, especially at times when I was in severe pain). Malone-Lee took me seriously, appeared genuinely concerned and even shocked at my previous treatment. He asked further questions, and then reassured me what I probably should've realised all along, that I had an embedded UTI, that the dipstick and even culture tests for urine have a very high false negative rate, and put me on high doses of antibiotics. He emphasised that if I had any side effects at all, I should call him immediately and he would switch me to another antibiotic.

About 8 months later, after one switch of antibiotics, I started to recover! I woke up one morning and waited for the pain to kick in. It didn't!! And ever since then, thanks to the Professor and his regular checking system, altering my medication where necessary, my symptoms have been lessening (I only have a minor sensation of pain now, and some frequency, and am no longer on the Lyrica or Duloxetine). I am now able to look after my boys, work, and live a normal life. I am grateful for his reassurance that this condition takes "dogged persistence" (It certainly does!), grateful for his kind words of encouragement and so grateful for his amazing expertise, his dedication to his clinic and to all of his patients. He is a genius. I know some of the other patients personally now, and we all feel the same way. The Professor (and his team of lovely staff) saved my life and are continuing to look after me with such care on this journey of recovery. For that I will be grateful forever.

I wrote this before his clinic was suspended. I am now back on small doses of anti-anxiety medication simply at the thought of having to revert back to the pain I was once in, and the anxiety and depression that follows from the pain and from not being able to function. Should his clinic remain suspended I, along

with hundreds of other women face a difficult choice: either to self-medicate with antibiotics bought off the internet, because we know that without our medication we will not be able to live normal lives. Or pester our GP's for life long very strong pain killers. I know that many, left in severe pain, with no end in sight (ie. no-one with this specific expertise in treating embedded bladder infections with long term antibiotics because the short courses don't work for us), will have no option but to end their lives.

Patient Impact Statement

I have suffered from UTI symptoms since 2005. This condition has caused severe pain, left me unable to sleep, leave the house, or function at all. I have had extended periods of time off work. I have felt like my life is not worth living. My last relationship broke down due to the impossibility of having sexual relations. I have seen multiple general and specialist doctors and have been prescribed many short-term and low dose antibiotic therapies. Since being under Professor Malone-Lee's care, I have experienced significant improvement in my pain, frequency and other symptoms and have been able to live a normal life.

History and treatment received prior to being under the care of Professor Malone-Lee

In 2005 I suffered from symptoms of an acute UTI. I was treated with a short course of antibiotics. The symptoms worsened, and tests with my GP suggested the UTI wasn't cleared. I was prescribed another short course of antibiotics, which didn't work, then another. Finally the Dr said he couldn't help me, my urine had 'lots of bugs in it' and suggested I see a specialist.

I saw a gynaecologist who ordered a laparoscopy and cystoscopy, which showed no issues. After the op I was in severe pain and returned to the gynaecologist who said there was nothing wrong with me and I should "relax and have a glass of wine".

I was in constant pain, with unbearable urinary frequency, and struggled to leave the house. I returned to my GP, who prescribed painkillers and told me I would have to live with the symptoms.

The pain continued, so I saw another urologist (a leading specialist in the UK) who suggested further invasive tests (another cystoscopy and laparoscopy). I declined.

I saw a urogynaecologist, who ordered a urodynamics test and a urine cytology test, which suggested infection. I was prescribed low dose antibiotic treatments and anticholinergics**.** I tried acupuncture. I continued to suffer from pain, sleeplessness and frequency, often using the toilet every 10-15 minutes. My consultant was sympathetic but unable to help. Repeated tests suggested an infection but none of the treatments had any effect.

My relationship broke down as I was unable to have sex with my partner.

I started taking high doses of amitriptyline. I was too tired to function. I had extended time periods off work. I was also hospitalised and treated with IV antibiotics.

People describe me as a happy, optimistic person. But this condition left me desperate and wondering if life was worth living. Not having a diagnosis or any treatment options left me in despair. I even travelled to Russia and New York looking for answers.

Treatment under the care of Professor Malone-Lee

Finally, in 2007 I was referred to Professor Malone-Lee. During my first appointment (and subsequently) he went through all of my symptoms with a degree of thoroughness entirely lacking in many of my previous consultant appointments. He examined my urine under a microscope and saw white cells and other infection markers. After further testing he explained I had a chronic infection which had become embedded in the urothelium, which was treatable, so I finally had a diagnosis and some hope.

He prescribed me some antibiotics over a longer period. Every step of the way my treatment options were thoroughly reviewed and explained to me, with the potential benefits and risks. We discussed my symptoms, as the increase in infection markers often lagged behind my actual symptoms. It took a while, but eventually I began to show an improvement.

My care has been exemplary. Every member of the clinic team is professional and caring. I feel supported and they have given me my life back.

Over time my condition has slowly improved and I am now on a regimen that has given me many pain free periods. This last year has been my best since 2005. I got married. I could walk for more than 15 mins

without pain, attend exercise classes and even start working again. Any minor blips have been swiftly dealt with by the clinic, with a response rate of 24 hours.

Now

I was being treated for a flare when the clinic was suspended. A urine cytology test shows clear signs of an infection, which has now gone untreated for 2 weeks. I am in severe pain and I know from experience that the only team that can help me is Professor Malone-Lee's.

Patient Impact Statement

My bladder symptoms started on December 14 2013. Terrible bladder pressure and constant feeling of needing to go to the toilet.

My first port of call was my GP who tested my urine and said that there was no infection present. As I hadn't had an infection in 20 years, I thought maybe Thrush was causing the symptoms but tests were clear. After 2 more negative urine tests (which were sent off to be cultured) I had had symptoms for a month and it was seriously impacting my quality of life. I was constantly tearful and struggling to hold down my job as well as look after my young autistic son.

I heard about a clinic which tested for infection so saw them at the end of January 2014 and they found 3 different types of bacteria. Through the COB foundation I then found Professor Malone Lee and started treatment with him in April 2014.

He didn't look at me as if I was mad and totally believed that I was in pain and struggling and assured me that he could help. He was kind, caring and compassionate and I trusted him immediately. His team are all brilliant, from Marcia his wonderful secretary who always has a smile and makes you feel that she really cares how you are doing, to Harry and the girls in the lab examining the urine samples. The doctors who help the Prof, Dr Dhan and Dr Swarmy are equally lovely and supportive and it's just a fantastic team which is shown by how many of his patients are improving or living normal lives off antibiotics completely.

Over the last 18 months I have improved to 80% better than when I started with him and feel so much better than I did. However I am currently flaring and feel frightened and unsupported as I cannot speak to him and discuss my current pain which I know he would be able to sort out.

To be so dismissive of the Professor and what he has done for so many women when they had been let down and treated disgracefully by GPs and urologists is a travesty. My illness has a name – I have a chronic bladder biofilm infection and I was being treated successfully for it. Now, my future is very uncertain and I will almost probably relapse one my current supply of antibiotics run out and that terrifies me as I do not know how I will manage.

This illness can take you to the depths of despair and leave you feeling isolated, lonely and bereft of hope. You feel that you are the only person suffering with this and there is no way out of the pain and suffering. It is almost certainly life changing and life limiting in many ways.

Patient Impact Statement

During my life I have had urine infections but a change took place from around 2003 when I had a particularly bad urine infection and my GP for some reason gave me a short antibiotic course which led to my infection getting worse shortly after the course ended. I went to what was the emergency out of hours surgery at the hospital and was given more antibiotics.

I had further infections treated with short courses by my GPs over the years and finally 5 years ago the pain got worse but no bacteria were grown from urine tests even though I had white blood cells, epithelial cells and some red blood cells again intermittently. The pain was difficult to live with. Due to having prolapses I saw a Urogynecologist and also a Colorectal Surgeon as I also have an intussuscepted bowel. I told my Urogynecologist about my bladder pain but he said there was nothing wrong apart from a cystocele which should not be painful. I asked for further investigation into why I had so much pain from my bladder but he told me there was no reason to do this as my bladder was fine.

I saw a Gynaecologist who told me that my bladder pain had nothing to do with my prolapses, and all the time my GP kept testing my urine and occasionally giving me short antibiotic courses due to me having white blood cells in my urine but no bacteria could be grown from my urine.

I then went to another Urogynecologist who I had heard was good with bladders. After some time, I had my bladder investigated due to having red and white blood cells in my urine and the pain was getting worse and worse. I was given a flexible cystoscopy where a tube is put into the bladder with a camera. The nurse tried to put the tube into my urethra but was so swollen that it first went into my vagina so the nurse then firmly and painfully put the tube into my urethra which was very painful and possibly introduced more bacteria into my bladder as well.

This was when the infection in my bladder wall could be seen on the screen. The walls of my bladder were a coffee colour and the blood vessels were black. The nurse explained to me that I had follicular cystitis which had been caused by an infection not having been treated correctly for long enough resulting in chronic infection deep in my bladder wall and in my urethra. I bled for 5 days straight quite badly from the tube being inserted and when I called the hospital the nurse told me this was due to the inflammation from the infection in my bladder and urethra.

I was given antibiotics for a few weeks with no Hiprex but the infection got far worse and so did the excruciating pain. I found it hard to do anything and even getting to the hospital for my appts was very difficult. I felt suicidal with the pain that went on 24 hours a day and was impossible to sleep through. My children were scared by how much this affected me and my daughter did as much as she could around the house. My whole life was affected and my GP just didn't know what to do. When I went back to the Urogynecologist I asked her if maybe the antibiotic she gave me was the right one to kill the bacteria in my bladder wall and if the tube they used could have introduced more bugs. The Urogynecologist seemed annoyed that the treatment hadn't worked and told me she was scheduling me for a rigid cystoscopy and may give me steroids.

By now it was March 2014 and I was in so much pain I decided to see the Professor. I had heard of Professor Malone-Lee from being a member of the COB foundation and decided to see him to see if he could help me. I saw him at the Whittington Hospital and he told me he could help me and I started treatment with him straight away. I got better and better and this year I took my children on holiday am working more hours and living my life without the dreadful pain I was in before. I know it is a long road to being completely cured but I have my quality of life back and can look after my Son who is still at school. I cant go back to the excruciating pain I was in before treatment and will run out of antibiotics soon.

I believe it my human right to have my treatment continued. I don't believe it is legal to have my ongoing treatment taken off me with no other clinic in this country operating under the same protocol as Professor Malone-Lee.

Please help me to get the Professors clinic re opened under his own protocol

Patient Impact Statement

I have suffered with bladder pain on and off since I have been eight years old. I have been under the care of a Urologist .

My pain frequency became considerably worse in 2007. I started Cystastat installations which helped at first. During 2008 the Cystastat stopped helping and at this point the bladder and urethral pain I was in was unbearable. My family had to take care of my children and I had to move back in with my parents. After numerous visits to A&E I was given Tramadol and even this did not help. I felt like my bladder and urethra were on fire I felt like I was being torched with a Bunsen burner. I had this unbearable burning pain for months I could not cope with the pain and felt suicidal. What was the point in being here anymore when I was unable to care for my children and couldn't cope with the horrific pain I was in. After several more visits to A&E I was given intramuscular Morphine and started on antibiotics. They kept me in and the next day said I was probably suffering in from cystitis and there was nothing else they could do except help me control the pain, I was devastated at this point. I was put on Morphine patches for a while and then I was given Oramorph, Tramadol, Ibuprofen, Paracetamol and Cyclizine. I felt that my urologist was unhelpful, uncaring and very dismissive of the severity of my illness even sarcastically saying "well I suppose I could remove your bladder." This to a 27-year-old woman with a young family was the final straw.

I then had severe back pain, burning in the urethra and bladder and a higher frequency in toilet visits each and every one agonising. I then had a cystoscopy, biopsy MRI scan and kidney scan. I had a cystoscopy on 22/12/08 and was told that my bladder looked ok and I was PROBABLY suffering from interstitial cystitis

I was then referred to another urologist and pain consultant. During this time I had numerous infections and sometimes I had to send off 3 urine samples over a number of weeks until a positive infection was found. It was mostly the E. coli bug that was present. The pain consultant put me on Pregablin but I struggled on this as I had muscle weakness and swelling of my hands and feet and severe tiredness.

I suffered at this point EVERY minute of EVERY day. I could not walk unaided and couldn't take care of my children, I had had to stop working two jobs and I was severely depressed and unable to cope. I saw numerous psychologists to help me deal with my depression and anxiety and was placed on numerous types of antidepressants. I could not wash myself, dress myself, cook for myself I had extreme fatigue from all the painkillers I was taking I had no motivation whatsoever.

Eventually urologists were not able to help me any longer as they didnt know what else to do. My parents paid for me privately to go and see a pelvic pain specialist in London. He referred me to professor Malone-Lee and other specialists. On the 6/4/09 I first visited the professor. The day I met the professor was one of the BEST days of my life as he gave me hope. He explained to me that I was not alone and EVENTUALLY with his help my pain and frequency would ease. When I left his office I collapsed hysterically as he was the only person who had given me hope for the future. He had given me hope that in the future I would be able to get my life back.

The condition I have is a chronic disabling condition which numerous experts had tried to treat. Professor put me on long term antibiotics alongside tablets to help with continence and pain relief. Slowly my condition started to ease. Instead of having the pain all day every day I now have breaks in between the pain giving me a much better quality of life. I am sure if my treatment was to continue eventually my pain would ease even more. The professor has always been there if I needed him or if I had any queries about my pain or medication. This man is an Angel from heaven, this man has given me my life back and by taking this man away from me you are handing out a death sentence, Without the antibiotics long term my pain will become worse. I am going to end up back where I started going back to A&E on mega strong painkillers and unable to cope.

I have felt like I haven't been taken seriously and I was making my illness up until I met he Professor. The professor or a member of his team are always there to give advice or to change my medication when needed. I have always been informed of the risks involved in taking long term antibiotics but this is the only way I have been able to have any quality of life. People with cystic fibrosis are given long term antibiotics to give them a better quality of life so why can't I?

Patient Impact Statement

October 2014	UTI urine test showing infection. 7 day course of antibiotics.
October– December	Return to GP four times – three more tests showing no infection.
January – February 2015	Increasing discomfort and then pain. Ultrasound scan clear. Only treatment offered Vagifem (local oestrogen) and pain killers
February 2015	A& E Guys and Tommys – given strong pain killers and short course antibiotic
February 2015	Unable to work. Pain increased, given stronger pain killers. Offered and declined antidepressants.
February 2015	Uro-gynae appointment. Internal scan clear. Told I might have tumour or Interstitial Cystitis (painful bladder syndrome). Offered and declined cystoscopy and told I couldn't have diagnosis or referral to pelvic pain clinic unless I had one.
March 2015	Appointment with Professor Malone Lee who diagnosed chronic infection and prescribed long term antibiotics. He explained I have inflammation of bladder and urethra with sphincter muscles cramping- caused by untreated infection. This happens after every bladder void. As I had an earlier history as a child of UTIs and then in my early 30s, it is likely I have infection embedded in bladder lining. Given Amitriptyline to help with pain.
June 2015	After very long wait, get appointment at National Hospital in London with specialist pelvic pain clinic. Offered and booked nerve block.
March 2015 – November 2015	Regular reviews with Professor Malone Lee every eight weeks liaising with my GP. Make very slow but steady progress with lessening symptoms. Cancel my nerve block appointment.

This year has very nearly broken me. I have been unable to work for seven months. I became increasingly distressed and depressed. Until June 2015 I could hardly go out. It often hurt to walk. I have had to take painkillers, sit on hot water bottles or use ice packs for relief. Symptoms changed every day and within a day – pain, discomfort, soreness, over active bladder, leaking, not getting to the toilet in time. I spent many days in tears. This condition has an impact on physical and mental health. It destroys career, social and family life. It is only in the last two months that I have begun to feel like myself again and travel further – I always have pain killers and ice packs ready in case I need them. My next appointment with Professor Malone Lee was 2nd November. I always count the weeks and days to these appointments, and now I am left without support, prescriptions or advice.

DEPUTATION STATEMENT

on behalf of the Patients of the LUTS Clinic, Whittington Health

APPENDIX J

Antibiotic Therapy

For

Occult Bacterial Bladder Infections (OBBI)

In support of patients of Professor Malone-Lee

Table of contents

Antibiotic Therapy for Occult Bacterial Bladder Infections (OBBI)

(1) Introduction

Urinary tract infection (UTI) is described as one of the most common infectious diseases in humans (1-2). Recurrent or chronic forms of this disease, described under the collective term 'Lower urinary tract symptoms' (LUTS) **(Figure 1)** are a major source of morbidity and mortality, particularly in females of all age groups (2-4).

Acute bacterial UTI is a straightforward clinical diagnosis. When faced with LUTS patients, however, clinical guidelines advocate that bacterial infection is excluded, given that much of the symptomatology overlaps with acute UTI (5-8). Therefore, the medical community widely defines the syndromes associated with chronic LUTS as 'infection-free', and condemns antibiotic treatment for these conditions.

The traditionally accepted paradigm of urinary infection assumes that bacteria ascend the urethra from the gut or vaginal reservoirs, resulting in extracellular colonization of the bladder and urine, with recurrent UTIs simply occurring due to re-infection (9). Early observations that identical bacterial strains were isolated in every episode of recurrent UTI suggest that there might be a latent, chronic infection periodically flaring up, undetectable by routine microbiological techniques (10-11).

The discovery of intracellular bacterial communities has revealed a mechanism whereby uropathogenic *Escherichia coli* (UPEC), as well as many other species, are able to invade superficial urothelial cells that line the bladder, allowing them to persist despite potent antibiotic treatments and immune defense mechanisms (10, 12). These pathological processes have now been shown to underlie, at least in part, most syndromes associated with chronic LUTS (13-17). A key prediction arising from these observations is that antibiotic treatment will help to resolve LUTS (18-23).

However, it is widely recognized that the very tests used to exclude urinary infection in routine clinical practice are largely inadequate (24). It is now clear that a significant portion of chronic LUTS patients may have been misdiagnosed and mistakenly led down a long pathway of invasive investigations and ineffective treatments, including complex urodynamics, cystoscopy, urethral dilatation, cauterization, physiotherapy, bladder instillations, with some even resorting to ileal conduit surgery. It is estimated that many thousands of patients have been failed by conventional therapies. It follows that routine microbiological methods advocated in clinical guidelines to identify urinary infections should be urgently reviewed.

Chronic urinary infections are notoriously difficult to treat, with biofilm infections almost impossible to eradicate with short-term antibiotics (25-31). It is now known that higher doses of antibiotics are required long-term, in tailor-made combinations, in order to achieve adequate tissue penetration to eradicate these persistent polymicrobial urine infections.

This review will examine the available evidence published in peer-reviewed scientific and clinical literature to determine: the persistence of uropathogenic organisms in intracellular bacterial communities; the infective pathophysiology of

chronic LUTS syndromes; the efficacy of antibiotic therapy in treating LUTS; the rationale for antibiotic selection in treating LUTS; and the margin of safety to which these agents can be used. *In* vitro, *in vivo* and clinical data highlighting the invasive and persistent nature of urinary infections will be analyzed, and the numerous trials where antibiotics have been used at high doses for protracted periods of time will be reviewed.

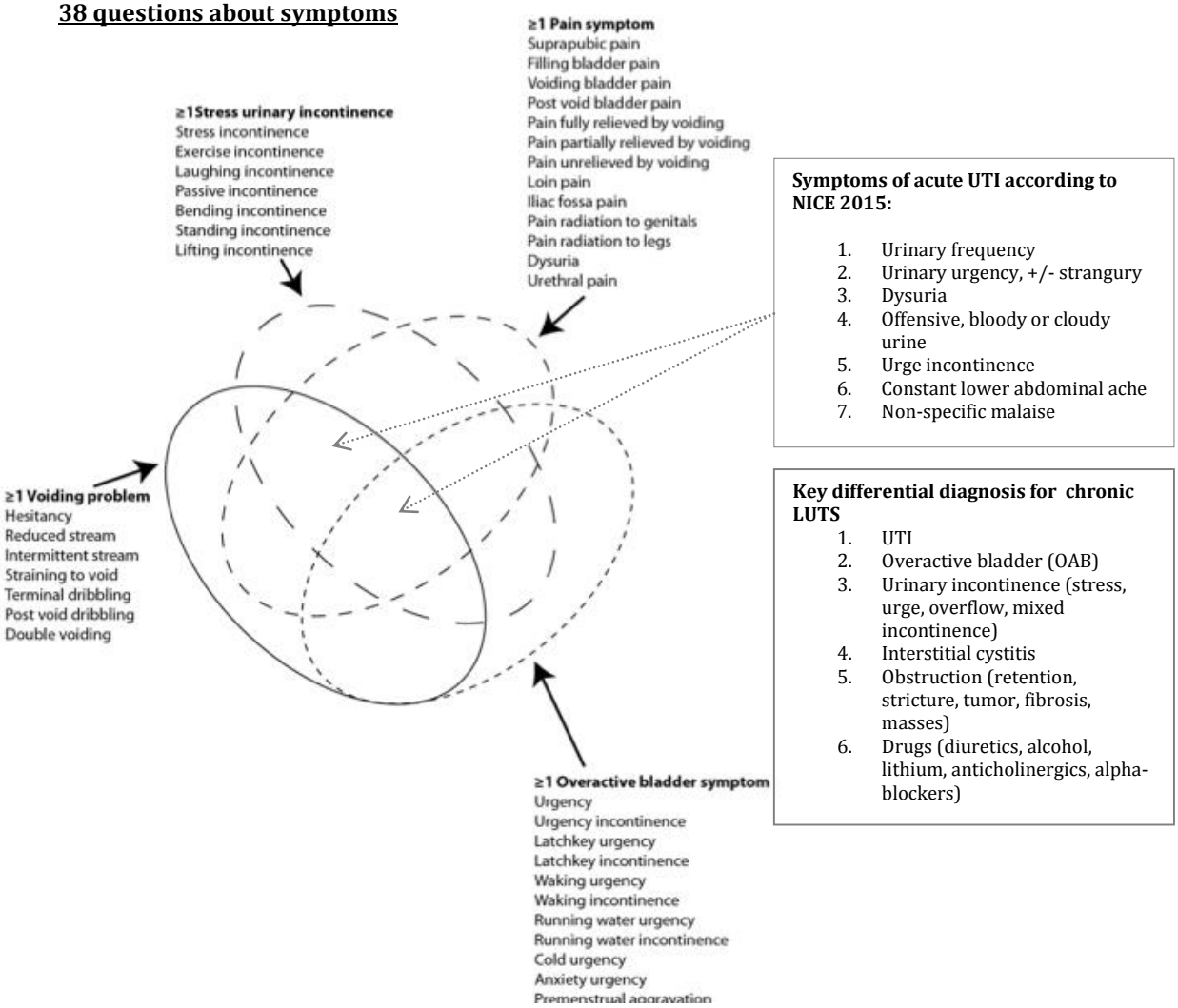

Figure 1- A simple 38-item symptoms scale to assess LUTS validated by the International Continence Society, adapted from (4).

(2) Missed diagnoses of occult bacterial bladder infections in LUTS patients

In all patients with acute dysuric symptoms, current medical practice involves initial urinary dipstick testing for leucocyte esterase and nitrites. If acute symptoms are typical, a mid-stream, clean catch urine sample may be sent for culture, despite negative dipstick results. If the symptoms are equivocal (commonly occurring in chronic, non-dysuric LUTS patients) and the initial urinary dipstick is negative, the sample may not be sent for culture at all (32).

A striking meta-analysis in over 95,000 children with acute dysuria showed that no rapid diagnostic test could reliably identify or exclude infection preceding urinary culture (33). Urine culture also has substantial limitations (24, 34). For largely historical reasons, the gold standard has long been defined as bacterial growth of a single organism at more than 10^5 CFU/ml, with epithelial cells indicating contamination from the perineum (35-36). The 10^5 CFU/ml threshold was set out by Kass in 1957, and is widely criticized, as his patients' urine samples were collected from only 74 women with acute fulminant kidney infections, with bacteria thriving in their urine. Since the late 1950's there have been reports that such a threshold is not sufficiently sensitive to pick up all urinary infections, but the concerns of numerous scholars have been largely ignored by the medical community (37-44). In early reports, Stamm and colleagues have demonstrated that the threshold set out by Kass can only pick up 50% of urinary tract infections. They proposed a more sensitive diagnostic criterion of 10^2 CFU/ml, which has been supported by many others, including J. Malone-Lee and colleagues in recent studies. It should also be noted that "mixed growth" culture with evidence of epithelial shedding, in the context of symptomatic, pyuric patients, point to a very significant pathological state, and should not be dismissed as "contaminated samples" (44-45).

We have recently seen a resurgence in the interest in the poor sensitivity of these diagnostic tests. Key studies are summarized in **Tables 1(a) and 1(b).**

It is clear from the evidence presented below that the assumption of no infection in chronic LUTS patients cannot be made based on negative results on routine diagnostic testing. Because of the poor sensitivity of these tests, it is very concerning that many thousands of patients with LUTS may have been incorrectly labeled as infection-free, and potentially misdiagnosed altogether. The concept that occult infection may at least in part be responsible for LUTS is sensible, as the symptoms greatly overlap with those of UTI, and many of these patients have suffered a period of confirmed recurrent UTI, and persistently demonstrate signs of inflammation in their urine. The next section of this review will focus on the evidence for this proposition.

Novel markers of infection and more sensitive microbiological techniques exist, but are not feasible for use in routine clinical practice (46-51). Immediate microscopic examination for pyuria and urothelial shedding is also time-consuming and therefore not widely applicable. Until adequate methods are found, the best clinical indicator of occult infection is probably assessment of symptoms, using a standardized, validated scale (52-55).

Study	Description	Findings
Khan 2008 (56)	1. 90 female patients with overactive bladders provided MSU samples with pyuria of >6 WBC/ microliter 2. The study measured the timed decay of white cells in urine samples stored at room temperature, compared to refrigeration at 4^0C.	• In the samples stored at room temperature, WBC decreased to 60% in the first two hours • In refrigerated samples. WBC decreased to about 80% of the original during the first two hours. Therefore lysis of white cells is not significantly retarded by storage at 4^0C. • The only solution seems to be immediate microscopic examination in the clinic at the time of collection.
Sathiananthamoorthy 2012 (44)	1. 6208 LUTS patients and 43 controls provided MSU 2. Fresh urine specimens were examined by dipstick and microscopically to quantify pyuria and urothelial cells. 3. LUTS no growth, LUTS mixed growth, LUTS positive culture, and normal controls were compared to assess the significance of 'mixed growth culture' against symptoms, dipstick, pyuria, and urothelial cell shedding.	• LUTS mixed-growth and LUTS no growth showed markedly higher pyuria compared to normal controls, with LUTS positive culture being the highest. • Leucocyte esterase dipstick were positive in 4% of normal controls, 26% of LUTS no growth, 40% of LUTS mixed growth, and 36% of LUTS positive culture. • Nitrite dipstick were positive for 0 normal controls, 1% LUTS no growth, 11% LUTS mixed growth, and 9% LUTS positive culture.
Malone-Lee 2007 (57)	1. From 2003-2007, 788 patients with overactive bladder provided MSU samples 2, Fresh, unspun MSU specimens were studied by dipstick and microscopy using a haemocytometer chamber to assess the prevalence of pyuria in $\geq$10 wbc/ul in patients with overactive bladder. 3. Data were collected at initial presentation and following antibiotic treatment. The microscopy result for pyuria (>10 wbc/ul) was used as a reference gold standard.	• 58% LUTS patients showed significant pyuria at presentation. 74% patients demonstrated significant pyuria during the observation period. • 82% of patients with pyuria were positive with leucocyte esterase dipstick. The nitrite dipstick test was positive in only 8% of patients with significant pyuria. • Only 10% of patients presenting with pyuria produced a significant urine culture at $\geq 10^5$ cfu/ml • The origins of the inflammatory reaction in thee patients require elucidation, although chronic low-grade infection is a plausible option.
Stamm 1982 (37)	1. 187 women presenting with acute dysuria and frequency were included in this study. 2. 72 patients provided suprapubic aspiration, and 115 provided urethral catheterization samples, for comparison with MSU clean catch specimens.	• Defining UTI as $\geq 10^5$ cfu/ml results in an unacceptably low sensitivity of 50% in population of women with acute UTI. • In urine with colony counts less than $\geq 10^5$, pyuria closely correlates with symptomatic infection. • In women with acute UTI, the use of the diagnostic criterion of 10^2cfu/ml gram-negative bacilli result in a sensitivity of 95% and specificity of 85% indicating infection.

Table 1 (a)- Key studies reporting the inadequacy of rapid urinalysis in clinical practice.

Study	Description	Findings
Khasriya 2010 (58)	1. Prospective blinded observational cohort study of 508 patients with painless LUTS symptoms. 2. MSU samples used to compare leukocyte esterase, nitrite dipstick and urine microscopy, with cultures at10^5 cfu/ml threshold 3. The above was repeated with 470 catheter samples (CSU).	• MSU culture at 10^5 cfu/ml was 56% sensitive, with 66% specificity • MSU nitrite was 10% sensitive, with 99% specificity. • MSU Microscopic pyuria was 56% sensitive, 72% specificity. • CSU culture at 10^5 was 15% sensitive, while enhanced culture at 10^2 cfu/ml was 29% sensitive. • CSU leukocyte esterase was 59% sensitive, 84% specificity. • CSU nitrite was 20% sensitive, 97% specificity. • CSU microscopic pyuria was 66% sensitive, 73% specificity.
Kupelian 2013 (59)	1. Prospective observational study of 1223 chronic LUTS patients between 2008-2011 (120 men, 1103 women) with LUTS 2. All patients provided MSU samples for analysis- to compare routine microbiological cultures, dipstick leucocyte esterase, and the influence of sample storage handling and processing on test performance.	• Positive predictive value and negative predictive value of pyuria as a surrogate marker of UTI were 0.40 and 0.75 • The dipstick was unable to identify significant microscopic pyuria (>10 wbc/microliter) in 60% f the samples, as defined by bacterial culture. • Refrigeration and preservation with boric acid retarded leucocyte decay, but 40% cells were still lost by 4 hours. • The use of staining (Sternheimer-Malbin protocol) to enhance inflammatory cells proved ineffective, with no difference between stained and unstained cell counts. • In conclusion, immediate microscopic examination for pyuria of unstained urine at the time of collection is warranted.
Williams 2010 (33)	1. Meta-analysis of 95 studies in 95703 children 2. Urine culture results were compared with rapid tests in children to establish whether rapid urine tests (microscopy for bacteria and white cells, dipstick urine) are significantly sensitive to guide early diagnosis of UTI.	• Microscopic examination of urine for detection of bacteria after Gram stain is the most accurate test, compared with reference standard urine culture. (sensitivity 91% and specificity 96%). However this should not be used to replace urine culture. • Dipstick testing for nitrites and leucocute esterase has a sensitivity of 88%. A dipstick should be interpreted as positive if *either* nitrites or leucocyte esterase is positive. • Leukocyte esterase detected by dipstick is as accurate as microscopy for white cells. • No rapid urine test is sufficiently sensitive to identify all children with UTI without the need for urine culture. Gram stain of bacteria has an estimated false negative rate of 9% which is unacceptably high. • If clinicians wish to identify all children with urinary tract infections, then a urine culture is always needed, irrespective of dipstick and microscopy result.

Table 1 (b)- Key studies reporting the inadequacy of rapid urinalysis in clinical practice.

(3) *In vitro* and *in vivo* evidence of cellular invasion by uropathogenic bacteria

The first studies to report intracellular colonization by uropathogenic bacteria date back to the 1980s (60-61). More recent studies demonstrated that specific strains of uropathogenic *Escherichia coli* (UPEC) are capable of forming intracellular bacterial communities within the cytoplasm of urothelial cells in humans, mouse models and in cultured urothelial cell lines (62). It was later shown that other species frequently implicated in UTIs possess similar invasive properties (17). The evidence of intracellular invasion in mouse models of acute UTI, *in vitro* bladder cell lines, and one study on 80 females with acute UTI is summarized in **Tables 2a, 2b, 2c, 2d.**

Intracellular bacterial communities serve to protect bacteria from antibiotics and immune responses, allowing low-grade persistent infection capable of reactivation (62). UPEC infection induces massive exfoliation of the urothelium in an effort to remove bacteria bound to these cells, but this can overcome by the ability of UPEC to re-invade the regenerated layer of urothelium after "fluxing" (63). In addition, antibiotics and neutrophils are often unable to penetrate intracellular niches, allowing UPEC maintain high bacterial titers (64-66). Schilling and colleagues have in fact shown that significant bacterial titers in confirmed intracellular bladder infections can persist despite treatment with antibiotics. (66). A recent study of patients with recurrent UTI revealed that their neutrophils displayed reduced levels of CD16, decreased bacterial phagocytosis, and lowered generation of reactive oxygen intermediates (67).

The intracellular lifecycle of UPEC is briefly summarized below (62):

1. To colonize the urothelium, UPEC exploit its structural biology. To preserve structural integrity during bladder expansion and contraction, urothelial cells naturally express uroplakins on their surface, assembled in hexameric rings, which add strength (68). In addition, uroplakin-coated vesicles reside beneath the surface, ready to fuse with the membrane to increase the membrane surface area on bladder expansion (68). UPEC express adhesins as part of a rigid pilus. An example is type 1 pili, which incorporate FimH at the distal tip, which bind to mannosylated residues of the urothelium (69). The tips of UPEC type 1 pili bury themselves in the central cavity of these uroplakin hexameric rings (62).

2. UPEC quickly invade the urothelial cells after attachment, and replicate rapidly in the cytoplasm of the host cell, maintaining their rod shape in loosely organized clusters, termed early intracellular bacterial communities (65).

3. Some hours later, a mature biofilm-like community emerges, and the rate of bacterial replication slows (65). During this phase, the surface of infected urothelium reveals large protrusions (70).

4. In a process which resembles the viral lytic cycle, the bacteria burst out into the bladder lumen in a process termed 'fluxing (71)'. They adopt a rod morphology, become highly motile, and often become highly filamentous (65).

5. Many of the surviving bacteria reinvade and undergo a new generation of intracellular community formation (65). These bacteria appear to be in a dormant state, neither dividing nor progressing through the same cascade (65).

Study	Description	Findings
Anderson 2003 (70)	1. Mouse models of acute UTI inoculated with clinically isolated UPEC strains. 2. Scanning electron microscopy of infected bladders to visualize colonies and structure. 3. Confocal microscopy to demonstrate accumulations of bacteria underneath the uroplakin-expressing urothelial cells.	• 24h post infection, UPEC strains mature into a uniform coccoid morphology from previous loose collections of rods. • UPEC organize into tightly packed intracellular biofilms. • UPEC accumulate within the cytoplasm, with electron-lucent halo surrounding the bacterium. • Biofilms form pod-like bulges on bladder surface, thus forming a persistent reservoir, AND Bacterial colonies extend above the luminal surface. • FimH mutations abolish this pathogenic pathway.
Mulvey 2001 (71)	1. Mouse models of acute UTI inoculated with clinically isolated UPEC strains. 2. Histological examination of infected bladders and exfoliated urothelial cells to demonstrate penetration by UPEC. 3. Antibiotic protection assays to demonstrate persistence and reemergence of intracellular bacteria from infected epithelial cells.	• Type 1-piliated uropathogens can invade the superficial epithelial cells that line the luminal surface of the bladder and replicate, forming massive foci of intracellular *E. coli.* • The bacteria were elongated, colonizing adjaecent superficial as well as deeper host cells to avoid exfoliation. • Bacteria in intracellular niches create chronic quiescent reservoir in the bladder to avoid clearance by exfoliation and urine flow. • Persist undetected for several months without bacteria shedding into the urine.
Schilling 2002 (66)	1. Mouse models of acute UTI inoculated with UPEC strain. 2. 10 days Trimethoprim-sulfamethoxazole antibiotic therapy of mice 3. DNA fingerprinting	• 3 of 14 inoculated mice had more than one recurrence during 6-week period. • UPEC reservoirs developed in faeces and bladder • 10 day antibiotic therapy reduces recurrence, while 3 days therapy has no effect. • 10 day antibiotic therapy did not eradicate bacteria from the bladder reservoir.
Rosen 2007 (13)	**1. 80 young healthy females with acute UTI and 20 asymptomatic females with history of UTI** **2. MSU clean catch specimens** **3. Light microscopy, immunofluorescence, electron microscopy to demonstrate intracellular (in uroplakin positive epithelial cells) or filamentous bacteria**	**14 of 80 with UTI showed evidence of intracellular bacteria, all of which were filamentous.** **All 14 intracellular bacteria were in *E. coli* infected urine. None of the gram positive had intracellular or filamentous bacteria.** **33 of 80 showed evidence of filamentous bacteria.** **None of the asymptomatic females showed evidence of intracellular bacteria or filaments.** **Electron microscopy large spherical biofilm collections of bacteria, of coccoid morphology, similar to those observed in mouse studies.** **Urine cytology observed in human and mouse UTI were indistinguishable**

Table 2 (a)- Key studies reporting the formation of intracellular bacterial communities of uropathogens.

Study	Description	Findings
Mysorekar 2006 (72)	1. Mouse models of acute UTI inoculated with clinically isolated UPEC strains. 2. Mouse bladders were removed and examined for microscopy, histology and colony-forming-units (CFU) titration.	• UPEC establish quiescent intracellular reservoirs within Lamp1+ endosomes of superficial facet cells. • PS treatment induces exfoliation of superficial facet cells, which eliminates quiescent intracellular rosettes localized to these cells. • Quiescent intracellular rosettes form within underlying transitional cells in PS-treated bladders, damaging the superficial facet cells. • Transitional cell intracellular bacteria are also enclosed in Lamp1+ endosomes. • Bladder epithelial turnover is associated with reemergence of UPEC from the reservoir.
Garofalo 2007 (73)	1. Mouse models of acute UTI inoculated with 18 clinically isolated UPEC strains from acute and recurrent cystitis patients. 2. Mouse bladders were removed 6h and 24h post inoculation. 3. PCR studies to detect virulence factors in UPEC strains. 4. Western blotting to detect PapA and FimH proteins 5. Haemagglutination assays to detect bacterial adhesins. 6. Confocal microscopy to detect intracellular bacterial communities.	• FimH expressed in all isolates. • Type 1 pilus production in clinical isolates. Type 1-mediated Haemagglutination was inhibited by exogenous mannose in first event acute UTI strains. In recurrent UTI isolates, the titers could not be entirely inhibited by exogenous mannose, due to expression of mannose-resistant adhesin system. • 3 of the 4 acute UTI UPEC isolates, and 4 of the five recurrent UTI UPEC isolates formed intracellular bacterial communities. • Isolate-specific differences in the time course of intracellular bacterial community formation (3h-24h). • Isolates from women with asymptomatic bacteruria, acute UTI and recurrent UTI and pyelonephritis formed intracellular bacterial communities. • UPEC isolates which were unable to form intracellular communities alone, were able to do so in mixed infections where the second isolate is a competent strain. • Isolates that were unable to form intracellular bacterial community were deficient in invasion of the urothelium.
Elliott 1985 (60)	1. Tissue biopsy obtained from 33 patients with LUTS studies with microbiological techniques and electron microscopy. 2. All LUTS patients had not responded to antibiotic therapy completely.	• Bacteria isolated from biopsy from 8 of 16 patients with sterile urine • Bacteria seen in urothelium in 14 of 16 patients with sterile urine. • 11 patients had 10^8 CFU in culture, all of which showed bacteria in the urothelium. • Urothelium grossly disrupted with loss of epithelial cells, when compared to normal, uninfected bladders.

Table 2 (b)- Key studies reporting the formation of intracellular bacterial communities of uropathogens.

Study	Description	Findings
Rosen 2008 (74)	1. Mouse models of acute UTI inoculated with UPEC and *Klebsiella pneumoniae* strains. 2. Antibiotic protection assays to determine the ability of UPEC and *Klebsiella pneumoniae* to invade urothelial cells. 3. Histology to analyze intracellular bacterial community formation.	• UPEC and *K. pneumoniae* had substantial intracellular populations of bacteria at both 6 and 24h post-infection. • Number of intracellular and extracellular bacteria were significantly lower for *K. pneumoniae* strains than UPEC • History showed large biofilm-like intracellular communities in *K. pneumoniae* infected bladders • Antibody-targeted staining confirmed that type 1 pili are expressed within both *K. pneumoniae* and UPEC. • Filamentous bacteria were found at 24h post infection in both *K. pneumoniae* and UPEC infected samples.
Justice 2004 (65)	1. Mouse models of acute UTI were infected with UPEC strains, and the bladders were harvested 2-6 hours post infection. 2. Time-lapse video microscopy was used to observe live the lifecycle of UPEC in infected mouse bladders	• In its intracellular life cycle, UPEC progresses through four distinct developmental stages. • Phase 1: intracellular bacteria are non-motile, rod shape, rapidly grow in loose colonies free in the cytoplasm of the superficial bladder cells. • Phase 2: collection of intracellular bacteria mature into slow growing, highly organized biofilm community consisting of coccoid bacteria, filling most of the cytoplasm. • Phase 3: switch to motile rod shaped bacteria allowing detachment from the intracellular community and fluxing out of the cell • Phase 4: bacteria are filamentous, and re-enter the intracellular bacterial community of the superficial urothelial cells to form a quiescent reservoir, to persist in the urinary tract.
Szabados 2008	1. Cell culture of human urinary bladder cell lines infected with *Staphylococcus saprophyticus, Staphylococcus areus, Staphylococcus epidermidis, Staphylococcus carnosus* and UPEC. 2. Fluorescence-activated cell sorting assays (FACS), antibiotic protection assays, and electron microscopy used to determine invasive properties of *Staphylococcus* strains and UPEC, in human urinary bladder cell culture.	• FACS assay showed staphylococcal invasion with very few adherent *S. saprophyticus* found. This shows that adherence does not influence the internalization measurement in *S. saprophyticus*, and that the mechanism of invasion in *Staphylococci* may be different to that described for UPEC. • *Staphylococcus saprophyticus* was significantly internalized in the antibiotic assay. • Electron microscopy shows that *S. saprophyticus* was documented to be inside the bladder cells, and the pictures bear striking similarities to internalized UPEC strains.

Table 2 (c)- Key studies reporting the formation of intracellular bacterial communities of uropathogens.

Study	Description	Findings
Berry 2009 (76)	1. Gentamicin protection assay and fluorescence microscopy to study *in in* vitro model of UPEC proliferation within immortalized human urothelial cells. 2. Pharmacologic manipulation of urothelial cells with cholesterol-sequestering drug Filipin to determine the effect of lipid rafts on intracellular proliferation and invasion of UPEC. 3. Real-time PCR with RNA harvested from intracellular UPEC to determine the gene expression profile.	• UPEC Is capable of intracellular proliferation in bladder cells *in vitro* in antibiotic protection assays. • After 24h the numbers of intracellular bacteria were significantly increased than at 2h. A dual staining method for extracellular and intracellular bacteria prior to permeabilization confirmed that this increase was due to intracellular proliferation. • Electron microscopy at 24h post infection showed that intracellular bacteria were rod shaped, localized in the perinuclear space, spread throughout the cytoplasm. • 80% of infected cells contained 1-5 bacteria after 24h, 17.9% contained 6-20 bacteria, and 3.6% contained >20 bacteria. • Filipin enhances UPEC intracellular proliferation3-fold over 24h, while intracellular bacteria increased 8-fold. Filipin did not affect invasion. • Expression iron acquisition systems and putative virulence factors and biofilm adhesins were up regulated by intracellular UPEC.
Hultgren 1985 (77)	1. The growth of *E. coli* in mouse models of UTI was studied. 2. Heavily piliated *E. coli* strains were placed surgically in the peritoneum of mice, and in a separate group, inoculated into their bladders. 3. Pilliation at various time points was determined by electron microscopy. 4. Colony counts in bladder homogenates to determine whether piliation on colonizing the urothelium.	• Piliation decreased and by day 5 most were nonpiliated in intraperitoneally inoculated mice. • Piliated phase variants were significantly more effective in colonizing the bladder urothelium than nonpiliated. Antibody to type 1 pili prevented colonization. • Immunocytochemistry of bladder lavages revealed large number of type 1 piliated bacteria adhering to the bladder transitional cells • Electron microscopy confirmed the presence of piliated bacteria in associated with the bladder urothelium • The urine of mice colonized with piliated bacteria showed no growth in culture.
Martinez 2000 (78)	1. Electron microscopy to examine the ability of type 1 piliated *E. coli* strains to invade urothelial cells in *vitro* and the steps in this pathway.	• Type 1 pili mediated invasion into bladder epithelial cells • FimH-mediated invasion is dependent upon actin polymerization by the host cell. • Invasion requires distinct host cell signaling events to influence the host actin cytoskeletal network (protein tyrosine phosphorylation and PI 3-kinase activation).

Table 2 (d)- Key studies reporting the formation of intracellular bacterial communities of uropathogens.

(4) Clinical evidence of cellular invasion by uropathogenic bacteria in LUTS patients

Based on previous observations that uropathogenic microorganisms are capable of cellular invasion, J. Malone-Lee and colleagues have reported convincing evidence that similar pathogenic pathways occur in the bladders of chronic LUTS patients, despite most of them testing negative in routine urine cultures.

Khasriya et. al., utilized enhanced culture methods to demonstrate that both control and patient groups harbor mixed extracellular bacterial growth, contesting the traditional view that normal urine is sterile (79). It was also shown that patients with LUTS harbor a distinct flora of intracellular pathogenic microorganisms, while asymptomatic controls mainly harbor harmless, commensal bacteria. More importantly, only the bacteria isolated from within the cells of LUTS patients have the capacity to invade urothelial cells in culture.

Horsley et. al, have actually visualized intracellular bacteria in cultured urothelial cells using the specialized technique of confocal microscopy, confirming once again that intracellular bacterial communities exist in chronic LUTS patients, despite negative routine cultures (13). It was shown that the dominant uropathogenic species was in fact *Enterococcus* faecalis, which mimicked the pathological pathway previously described in UPEC. In this study, no strains of UPEC were capable of intracellular invasion, which instead demonstrated adherent extracellular colonization.

It is clear from these observations that the delicate balance in the bacterial flora of the bladder has been disturbed in the LUTS patient samples. It has long been known in other medical specialties, specifically in relation to the bowels, that disruption of normal commensal flora can lead to colonization by pathogenic microorganisms.

In a series of clinical observations by J. Malone-Lee and colleagues in a specialist LUTS clinic, it was determined that patients with LUTS shed a significant amount of urothelial cells detectable in urine (80). These cells are visible under light microscopy but are traditionally dismissed as vaginal/perineal contamination. Tagging these cells with a specific marker of Uroplakin-3 confirms that these cells originate from the bladder, and reflect an inflammatory response of the bladder to infection.

More sensitive culture techniques at 10^2 CFU using spun urinary sediment provide convincing evidence that LUTS patients suffer from occult bacterial infection (81). Inadequate treatment of UTI may actually promote the establishment chronic subclinical-grade infection and increase antimicrobial resistance in the remaining, partially treated infection. These reports call for a prompt reconsideration of guidelines for diagnosis of urinary tract infection. It follows from these reports that antibiotic therapy may be beneficial in the treatment in LUTS, specifically in light of significant pyuria and epithelial cell shedding.

Study	Description	Findings
Khasriya **2013** **(79)**	1. Large prospective study over 3-years. 2. Clean catch urine samples (MSU) collected from 165 LUTS patients and 47 controls; catheter urine samples (CSU) collected from 55 patients and 26 controls. (Total: 220 patients, 73 controls) 3. Pyuria determined using light microscopy. 4. Routine hospital urine culture of urine supernatant on chromogenic agar under aerobic conditions, using Kass criterion. 5. Sediment culture enriched for shed bladder epithelial cells 6. Antibiotic protection assay using cell sediment. 7. Urothelial cell line in culture to investigate invasive properties of 8 patient derived strains (2 *E coli.,* 2 *E. faecalis,* 2 *S. anginosus,* 2 *P. mirabilis*) and commensal strains (2 *L. gasseri*).	1. 40% of patients with MSU samples showed pyuria. There was no statistically significant pyuria in patients with catheter-collected samples. 2. Routine hospital culture under Kass criterion as unable to distinguish patients with LUTS from controls. 3. Sediment cultures reflecting extracellular bacterial colonization of CSU cohort showed different bacterial isolates in both control and patient groups. Extracellular *E. coli, Enterococcus spp., Staphylococcus spp., Streptococcus spp.* were found in both control and patient groups. *Proteus*, *Micrococcus* were found only in patients. 4. The cell count after cell lysis of shed epithelial cells reflects the amount of intracellular bacteria. The predominant bacterial species found inside the cells of symptomatic patients was *E.coli, E. faecalis, Strep. Anginosus,* and *Proteus_mirabilis.* Control cells mainly contained *Lactobacillus gasseri*. 5. Invasion assays showed that bacteria were competent to invade tissue culture cells, except in the case of *L. gasseri* from control patients.
Horsley **2013** **(16)**	1. 705 chronic LUTS patients provided MSU. 2. Microscopy to determine pyuria in fresh unspun samples. 3. Immunofluorescence studies to assess epithelial shedding, by targeting Uroplakin-III (UP3) glycoprotein, which are expressed solely on urothelial cell membranes. These samples were compared with vaginal swabs to ensure that all UP3- positive cells found originated solely from the bladder. 4. Confocal laser-scanning microscopy and 3D digital analyses of shed urothelial cells in LUTS patients and controls, to visualize intracellular colonization, membrane-bound bacteria and extracellular biofilms. 5. Bladder cell culture system infected with 5 strains of *E coli*, and 5 strains of *E. faecalis*, all isolated from (MSU-culture negative) LUTS patients. Invasive properties of bacteria assessed using confocal 3D microscopy.	1. 74% of patients were negative for infection on routine MSU culture at Kass criterion, and 26% were positive. 2. Significant urothelial shedding from the bladder of chronic 75% of LUTS patients and 17% controls. Epithelial shedding was found to correspond to the amount of pyuria and severity of infection. 3. LUTS patient-isolated *E. faecalis* invades cells in a cell culture model system. 4. Confocal analysis suggests that only *E. faecalis* exhibits cellular invasion. *E coli* formed adherent extracellular bacilli. There were also adherent extracellular coccoid *E. faecalis* 5. All 5 *E. coli* infected cells exhibited adhesion and colonization, although entirely extracellular, forming tightly packed extracellular biofilms on the cell surface. 6. *E. faecalis* was competent to invade urothelial cells, in loose diffuse clusters.

Table 3(a)- Key studies by J. Malone-Lee and colleagues, reporting the presence of bacterial intracellular uropathogens in chronic LUTS patients.

Study	Description	Findings
Horsley, Tuz, Collins **2013** **(80)**	1. MSU samples from 22 chronic LUTS patients were compared with vaginal swabs. 2. UP3 immunofluorescence used to distinguish cellular origin of epithelial cells in MSU samples.	1. The proportion of UP3-positive cells found in the urine of chronic LUTS patients were significant higher than that in the vagina. 2. Increased shedding of urothelial cells is associated with LUTS in women. As with studies of acute UTI in humans and mice, this innate immune response suggests inflammation by low-grade infection in LUTS. 3. This demonstrates that the vast majority of epithelial cells found in urine originate in the urinary tract, and so the presence of epithelial cells does not mean that the MSU is contaminated by vaginal contents.
Horsley **2011** **(82)**	1. Blinded, prospective, comparative, observational cohorts study of 228 patients presenting with overactive bladder symptoms, and 63 patients wthout OAB from 2010-2011. 2. MSU samples analyzed by microscopic epithelial cell count and white blood cell count using a haemocytometer, and then submitted for microbiological culture. 3. Compare urinary planktonic epithelial cell counts with other disease markers and between patient groups.	1. 13% patients demonstrated bacteruria at presentation. 2. During follow-up, it was noted that elevation in the epithelial cell counts persisted long after other markers of infection had settled. Perhaps urothelial cell shedding is a later manifestation of the disease process.
Gill **2010** **(83)**	1. A blinded observational study using CSU samples from 41 OAB patients and MSU samples from 23 controls, which were examined for pyuria and routine culture. 2. The centrifuged urinary samples were gram stained and examined to count the normal uroepithelial and clue cells. Clue cells exhibit bacterial adhesion with bacterial division at the site of adherence, and represent markers of infection.	1. Compared to controls, there is significantly increased colonization of cells associated with OAB with or without pyuria. 2.Detection of clue cells was much higher in those with negative urine cultures, which could indicate that bacterial adhesions militate against culture detection.
Khasriya **2009** **(81)**	1. Examine the CSU culture of spun urinary sediments obtained from urine samples taken from 66 OAB patients and 19 asymptomatic controls, with immediate microscopy of a specimen aliquot for white cell expression. 2. Spun urinary sediment samples were compared to the results of routine culture (at 10^5 cfu/ml threshold) of the same specimens and	1. Routine cultures (at 10^5 cfu/ml threshold) were positive in 15% patients, of which all had pyuria. 2. Enhanced culture at 10^2 cfu/ml threshold was positive for 26% of patients, where 92% had pyuria. 6 patients were positive for both routine and enhanced culture, and all of these had pyuria. 3. Using spun sediment cultures, controls grew only 10^2 cfu/ml. OAB patients with pyuria grew 10^4 cfu/ml. OAB patients without pyuria grew 10^3 cfu/ml.

Table 3(b)- Key studies by J. Malone-Lee and colleagues reporting the presence of inflammatory response and bacterial infection in patients with OAB.

Study	Description	Findings
Khasriya, Ismail, Wilson (a) **2011** **(84)**	1. *E. coli, E. faecalis, Strep . anginosus,* and *P. mirabilus* were isolated from patients with symptoms of OAB. An isolate of *Lactobacillus gaserri*, was obtained from a control. 2. Cell culture of bladder epithelial cell line was infected with the above isolates. 3. Antibiotic protection assay was performed to examine intracellular bacteria.	1. The average intracellular bacterial count were E*. coli* 1.8x10 cfu ml^{-1}, *E. faecalis* 1.02x10^{4}cfu ml^{-1}, *Strep. anginosus* 2.69x10^{3}cfu ml^{-1}, *Proteus. mirabilus* 3.20 x10^{3}cfu ml^{-1}, *Lactobacillus. Gaserri* 0 cfu ml^{-1}. These differences were statistically significant. 2. It is clear that UPEC is not the only pathogen capable of invasion, and it is demonstrated that these phenomena contribute to the pathology of OAB symptoms.
Khasriya, Ismail, Wilson (b) **2011** **(85)**	1. 23 women with OAB symptoms 2. Intracellular invasion assay on shed epithelial cells performed to determine intracellular bacterial communities. 3. 26 patients and 8 controls used chromogenic agar to provide immediate species identification.	1. After the extracellular bacterial population was eradicated, there was an immediate increase in colony counts post lysis from intracellular stores. 2. 53% of OAB samples showed evidence of intracellular bacterial colonization of the bladder epithelium. Only 13% of control samples showed the same. 3. The dominant bacteria were *E. faecalis, Strep. Agalactiae, Strep. Anginosus, E. coli* and *Proteis mirabillis.*
Khasriya **2008** **(86)**	1. 378 urine samples collected by CSU from 194 OAB patients. These were cultured in special study culture methods (at 10^{2} cfu/ml threshold), compared with routine culture at 10^{5} cfu/ml threshold.	1. Routine laboratory cultures were positive in 12%. The study culture methods isolated bacteria in 30%. 2. These data imply that bacterial infection may be frequently missed during the assessment of a patient with OAB.

Table 3(c)- Key studies by J. Malone-Lee and colleagues reporting the presence of inflammatory response and bacterial infection in patients with OAB.

(5) Clinical evidence of antibiotic efficacy in LUTS patients

As expected, most patients suffering with chronic LUTS were negative on routine cultures (18-20). Long-term treatment with antibiotics led to improvement of symptoms which were measured using a standardized, validated symptoms questionnaire. This was also related to a clearance in bacterial growth and pyuria following antibiotic treatment. These findings are supported in reports by other groups (21-23) who treated interstitial cystitis and OAB with antibiotics.

These studies are proof-of-concept studies, and a strong justification for a large-scale, randomized placebo controlled trial of antibiotic use in patients with OAB, pyuria, but negative urine culture. The medical community rightfully frowns on the unjustified use of antibiotics. However it is widely acknowledged that in instances where such use is justified it would be unethical to deny patients effective treatment. It is expected such a movement would be met with much resistance in the current medical climate, which aims to reduce prescriptions for both financial and public health concerns of antimicrobial resistance, as well as safety to the patients. At times, the stigma associated with antibiotics use is so strong, that patients may be denied treatment despite clear evidence.

The next section of this review will focus on the antibiotics used in the treatment of chronic LUTS as outlined in a **(Appendix 1)** developed by James Malone-Lee in the tertiary LUTS clinic. Their properties, rationale for their use in treating chronic LUTS and safety considerations will be examined in depth.

Study	Description	Findings
Gill 2011 (20)	1.An observational cohort study of 440 (380 females, 60 males) patients, conducted from 2003-2010. 2. 147 of these had OAB and pyuria, and were treated with antibiotics (primarily Nitrofurantoin and cephalexin) with antimuscarinics and bladder training. 2. 212 had OAB with no pyuria, and received only antimuscarinics and bladder retraining. 3. 81 had OAB but manifested pyuria later at subsequent follow-up, at which point antibiotics were commenced. 4. Treatment response was monitored by validated symptoms-scores of average 24 hour frequency and resolution of pyuria.	• At presentation, 75% of OAB patients with pyuria were MSU culture negative, 88% of OAB patients without pyuria were MSU culture negative and 85% of OAB patients who later developed pyuria were MSU culture negative. • There was significant improvement in all symptoms in all groups over the treatment period. • The OAB group who received antibiotic late at follow up, took the longest to recover but showed significant improvement on receiving antibiotics. • The OAB group, which never developed pyuria and received no antibiotics, recovered the fastest. This implies that infection is an important disease complication in the other OAB groups. • Antibiotic efficacy was demonstrated with clearance of pyuria in the OAB patient group with pyuria at presentation.
Kupelian, Collins, Swamy, Gill 2013 (19)	1. Prospective, blinded, observational cohort study including 15 patients with multiple sclerosis and OAB symptoms and 15 asymptomatic controls included. 2. Compare outcomes at baseline and at 12 months after treatment with antimicrobial therapy, which was continued until microscopy demonstrated clearance of pyuria or patient reported symptom control. Outcomes were assessed using a validated symptoms-scale. 3. All patients provided CSU samples while controls provided MSU. All samples were analyzed immediately for pyuria, culture of spun urinary sediment, and routine laboratory culture.	• 70% of patients demonstrated negative routine culture at baseline. • Antimicrobial therapy was associated with a reduction in bacterial growth and microscopic pyuria. • Patients demonstrated significant improvement in symptoms and quality of life measures. 93% reported a marked or moderate improvement in bladder function. • These data suggest that bacterial infection may contribute to the generation of OAB symptoms in patients with MS.
Swamy, Gill, Kupelian 2013 (18)	1. Between 2010-2012, 351 female patients with chronic LUTS were treated for a mean of 279 days with high dose oral antibiotics. .	• Regression analysis showed a significant reduction in the 24 hour frequency, urgency, and voiding symptoms, as well as a reduction in pyuria by the end of this study.

Table 4- Key studies by J. Malone-Lee and colleagues, reporting the effect of long-term, high dose antibiotic treatment in patients with chronic LUTS.

(6) Rationale for antibiotic selection in a treatment protocol for LUTS patients

Antibiotic prophylaxis with multiple low-dose antibiotics has been shown to be effective at reducing the rate of recurrent UTI during prophylaxis when compared to placebo. These findings were published in the *Cochrane Collaboration* review of 19 randomized controlled trials looking at 1120 healthy women(87). In the world of evidence-based medicine, a systematic review of randomized controlled trials is the Gold Standard of clinical evidence.

Notably, the same review demonstrated that recurrent UTI in the treated group of patients relapsed to match the placebo group when treatments were ceased. Two important conclusions can be drawn from this large-scale study. Firstly, that antibiotic treatment is able control flares in recurrent UTI and secondly that low-dose long-term regime is not sufficient to eradicate the causative agent to prevent further relapse(87).

Due to the intracellular nature of the uropathogens involved in this polymicrobial disease, the efficacy of treatment will depend on three factors: first, the ability of the antibiotic to penetrate the cell, in order to reach the intracellular bacterial communities; second, the ability to penetrate the biofilm; and third, the diverse antibiotic resistance patterns of the multiple bacteria colonizing the urothelium.

It follows that antibiotics with good tissue penetrance should be selected, which will accumulate in tissue at sufficient levels to kill the intracellular bacteria. Penetrance depends mainly on fat solubility of the drug and the presence of special channels on the cell surface that could act as gateways for the antibiotic(88)(89)(90)(91). The duration of exposure to a given antibiotic is also critical to achieve good tissue penetrance(92)(93). Antibiotics which accumulate in the urine, will be beneficial in eradicating extracellular bacteria, or intracellular bacteria entering their lytic phase to become released in the urine. Antibiotics vary markedly in terms of potencies, and the polymicrobial nature of these infections is known to exhibit differential patterns of antimicrobial resistance(94)(95)(96). It therefore follows that antibiotics must be issued in combinations to target the varied nature of these infections at high doses, and for long-term.

The section below will examine the ability of each of the antibiotics presented in a treatment for LUTS patients to: a) penetrate either the cell or the biofilm and b) accumulate in levels sufficient to kill intracellular bacteria **(Appendix 1)**

No treatment, not even placebo, comes without adverse effects. What has to be justified is the use of the intervention in light of the risk benefit analysis. The scientific evidence regarding the role of persistent occult bacterial bladder infection in LUTS is discussed in depth above. This evidence base is substantial, meaningful and significant. The weight of the evidence supports persistent infection, although other mechanisms may co-exist and the exact etiology may vary from patient to patient. Thus, while antibiotics are not always effective, the importance of providing patients with the opportunity to receive an adequate trial of antibiotic therapy is heightened by the lack of other effective treatment approaches.

This evidence review does not advocate that this is a complete review of how these drugs work to target intracellular bacteria. These outcomes are both outside the scope and the power of this review. Instead, we aim to address concerns over safety and relevance of these treatments. We shall be especially vigilant to pay particular attention to serious adverse effects, which in this review will be defined as irreversible organ damage, irreversible biochemical derangements, irreversible ototoxicity or nephrotoxicity and any adverse effects, which by virtue of their pathophysiology may be or are likely to result in a lethal outcome or significant disability.

6.1 First Line Treatments

Nitrofurantoin

Nitrofurantoin belongs to a pharmaceutical class of nitrofurans related to nitroimidazoles. These compounds can easily permeate the cell membrane via facilitated diffusion(97)(98). They need to be metabolized in sensitive bacteria and parasites to express their activity and do not accumulate in healthy cells in their active form, which makes them remarkably safe(99)(100). Moreover, nitrofurantoin is completely excreted by the kidneys reaching high concentrations in the bladder and largely bypassing the other tissues(101). *In vitro* and *in vivo* studies found nitrofurantoin to be effective at killing intracellular *E.coli* due to its high intracellular penetrance(96). It has been found that 94.4% of *E.Coli* strains in the United Kingdom are susceptible to nitrofurantoin(94).

The safety of long-term nitrofurantoin treatment has been comprehensively demonstrated in a myriad of clinical trials. Brumfitt and colleagues examined clinical data of 219 patients treated for recurrent UTI at the Royal Free Hospital. 110 female patients received nitrofurantoin macrocrystals (Macrobid) at 100mg once daily dose for 12 months(102). Adverse effects were experienced by 42 women and were classified as mild. 16 chose to discontinue treatment. No serious adverse effects were reported. The research group reported no lung or liver damage(102). In total, Brumfitt et al. conducted 4 clinical trials over 18 years to look into the efficacy and safety of long-term nitrofurantoin for recurrent urinary tract infections(103)(104)(105)(106). These data are summarized in **Table 5** below.

There have been rare case reports of pulmonary reactions to Nitrofurantoin treatment. These are summarized in **Table 6.**

We can conclude that nitrofurantoin is a safe and effective compound for the treatment of recurrent urinary tract infections. This, coupled with its high cellular penetrance and high level of bacterial susceptibility, makes it an ideal first-line choice antibiotic for the treatment of recalcitrant cystitis.

Author	Antibiotic	Patients	Design	Duration	Dose	Adverse effects	Comments
Brumfitt et al. 1998 (102)	Nitrofurantoin macrocrystals (Macrobid)	110	Case records from female patients with recurrent UTI based on 18 years of clinical data	12 months	100mg od	Nausea = 15 Abdominal pain = 4 Thrush = 6 Rash = 8 Sweating = 1 Faintness = 1 Headache 2 All adverse effects = 42 Treatment stopped = 16	Only mild adverse effects were reported. Treatment was discontinued by 16 out of 110 patients voluntarily. One incidence of finger tingling resolved on discontinuation. No serious adverse effects reported.
Brumfitt 1981 (103)	Nitrofurntoin +methenamine	43	Prevention of recurrent urinary infections in women: a comparative trial between nitrofurantoin and methenamine hippurate.	12 months	50mg bd	Nausea (8 mild, 6 moderate, 7 severe) Vomiting = 3 Headache = 1 Indigestion = 1	No serious adverse effects reported.
Nunez 1990 (107)	Nitrofurantoin	28	Macrocrystalline nitrofurantoin versus norfloxacin as treatment and prophylaxis in uncomplicated recurrent urinary tract infection.		100mg od	Nausea, headache, epigastralgia, and arthralgia/myalgia	No serious adverse effects reported.
Brumfitt 1985 (106)	Nitrofurantoin	48	A clinical comparison between Macrodantin and trimethoprim for prophylaxis in women with recurrent urinary infections.	12 months	100mg od	Nausea = 7 Diarrhoea = 1 Candidiasis = 1 Others = 3 (one report each of macrocytosis, tingling fingers, and mild reaction to alcohol on a single occasion) Rash = 2 Headache = 1 Fever = 1	No serious adverse effects reported.
Brumfitt 1991 (105)	Nitrofurantoin	50	Comparative Trial of Norfloxacin and Macrocrystalline Nitrofurantoin (Macrodantin) in the prophylaxis of recurrent urinary tract infection in women.	12 months	100mg od	Nausea = 6 Oral/vaginal candidiasis = 3	No serious adverse effects reported.
Brumfitt 1995 (104)	Nitrofurantoin	59	A comparative trial of low dose cefaclor and macrocrystalline nitrofurantoin in the prevention of recurrent urinary tract infection.		50mg od	Vaginal irritation and nausea	No serious adverse effects reported.
Kasanen et al. (108)	Nitrofurantoin Macrocrystals	72	Comparison of the Effect of Placebo, Methenamine Hippurate, Nitrofurantoin and Trimethoprim Alone	12 months	75mg od	Rash = 2 Nausea = 2 Abdominal Pain = 4 Headache = 1 Leucorrhoea = 1	No serious adverse effects reported
Carlsen et al. (109)	Nitrofurantoin	32	Comparison of long-term, low-dose pivmecillinam and nitrofurantoin in the control of recurrent urinary tract infection in children. An open, randomized, cross-over study.	6-10 months	1.5 mg/kg/d	Loss of appetite = 4 Indigestion = 3 Loose stools = 1 Constipation = 1 Tiredness = 2 Bad taste/difficulty swallowing = 2	Based on a 50kg patient dosages used by authors were as follows: 75mg/kg/d nitrofurantoin No serious adverse effects reported.

Table 5- Data from 1 pooled review and 7 clinical trials detailing the side effects and uses of nitrofurantoin. Long-term high dose nitrofurantoin regimen is safe. Side-effects reported across 300 women are largely limited to gastrointestinal upsets, non-specific constitutional symptoms and a few incidents of hypersensitivity and candidiasis. No serious adverse effects were reported in the examined studies.

Trimethoprim

Trimethoprim is a fat soluble antibiotic. This somewhat unique property ensures that it can readily permeate into many cells, making it an effective treatment option for intracellular bacterial infection(110)(111). Despite this, Schilling et al. demonstrated that co-trimoxazole, a mixture trimethoprim and sulphamethoxazole, administered to mice infected with uropathogenic *E.Coli* was unable to eradicate intracellular infection, even after 10 consecutive days of treatment(112). Thus longer course of therapy are warranted. Moreover, *E. coli* isolates in the United Kingdom are remarkably resistant to trimethoprim, with only half of bacteria being susceptible to the drug(94).

The safety and efficacy of long-term trimethoprim treatment has been widely demonstrated in many clinical trials. Some of these are summarised in **Table 6** below. We can conclude that trimethoprim is a safe and effective agent for the treatment of recurrent urinary tract infections. This coupled with its high cellular penetrance but counterweighed by frequent bacterial resistance makes it a suitable but limited first-line alternative to nitrofurantoin.

Author	Antibiotic	Patients	Design	Duration	Dose	Adverse effects	Comments
Brumfitt et al. 1983 (113)	Trimethoprim	20	Long-term prophylaxis of urinary infections in women: comparative trial of trimethoprim, methenamine hippurate and topical povidone-iodine.	12 months	100mg od	irritation/rash of vulva or vagina = 1	Only mild adverse effects reported. No serious adverse effects reported.
Seppane n 1988 (114)	Trimethoprim-sulphamethoxazole	12	Cinoxacin vs trimethoprim--safety and efficacy in the prophylaxis of uncomplicated urinary tract infections.	72 months	100mg od	Vaginal candidiasis = 1 Slightly elevated S-ALT value ("probably due to oral contraceptives") = 1 Transient rise in the eosinophil count = 1	Only mild adverse effects were reported. No serious adverse effects reported.
Brumfitt et al. 1985 (106)	Trimethoprim-sulphamethoxazole	38	A clinical comparison between Macrodantin and trimethoprim for prophylaxis in women with recurrent urinary infections	12 months	100mg od	Candidiasis = 4 Nausea = 4 Rash = 1 Diarrhoea = 1	Only mild adverse effects were reported. No serious adverse effects reported.
Stappleto n et al. 1990 (115)	Trimethoprim-sulphamethoxazole	16	Postcoital antimicrobial prophylaxis for recurrent urinary tract infection. A randomized, double-blind, placebo-controlled trial.	6+ months	100mg postcoital	Nausea = 1 Confirmed vaginal candidiasis = 1 Vaginal symptoms = 1	Only mild adverse effects were reported. No serious adverse effects reported.
Stamm et al. 1980 (116)	Trimethoprim	13	Antimicrobial prophylaxis of recurrent urinary tract infections : a double-blind, placebo-controlled trial.	6 months	100mg od	None	Authors: "Prophylaxis with these drugs is effective, well tolerated, and did not produce emergence of resistant E. coli but may predispose to non-E. coli urinary tract infections after its discontinuation."
Kasanen et al. (108)	Trimethoprim	77	Comparison of the Effect of Placebo, Methenamine Hippurate, Nitrofurantoin and Trimethoprim Alone	12 months	Trimetho prim 100mg od	Abdominal Pain = 1 Headache = 1 Fatigue = 1	No serious adverse effects reported

Table 6- Data from 6 clinical trials detailing the side effects and uses of trimethoprim. Long-term high dose trimethoprim regimen is safe. Side-effects are largely limited to

gastrointestinal upsets, non-specific constitutional symptoms and a few instances of candidiasis. No serious adverse effects were reported in the examined studies.

Cephalexin

Cephalexin belongs to a class of antibiotics known as cephalosporins. It is referred to as a first-generation cephalosporin as it is indeed one of the oldest antibiotics available from this class. First generation cephalosporins have good efficacy against gram-negative bacteria such as *E.coli*. *E.coli* is responsible for 75% of urinary tract infections in women(117). Cephalosporin is a bactericidal antibiotic, which means that it has the capacity to kill bacteria, rather than simply stop them from replicating.

This antibiotic has been widely used in the treatment of uncomplicated urinary tract infections. Numerous studies, also advocate its use as a high-dose long-term prophylactic agent in chronic bacterial prostatitis with a narrow side-effect profile(118)(119). One study, looking at children with cystic fibrosis went further and administered high-dose cephalexin to children for durations of up to 84 months(120). The doses employed in this study would translate to an adult equivalent of 4 grams of cephalexin daily. Out of the 119 participants in this study, only 19 discontinued the drug due to adverse effects and no serious adverse effects were mentioned by the authors. This and other evidence for the long-term use of cephalexin is presented in **Table 7** below. We can conclude that cephalexin is a safe and effective agent for the treatment of recurrent urinary tract infections.

Paulson and Colleagues

Paulson et al. treated 44 men with chronic bacterial prostatitis with cephalexin 500mg four times daily for 1 month. A total of 8 mild adverse effects were reported. There were no serious adverse effects in the treated group receiving 500mg four times daily(118).

Author	Antibiotic	Patients	Design	Duration	Dose	Adverse effects	Comments
Paulson et al. (118)	Cephalexin	44	Multicentre, single blind parallel group study of antibiotic therapy for chronic bacterial prostatitis	1 month	500mg qds	Nausea = 2 Vomiting = 1 Diarrhoea = 0.56 Headache = 1 Skin rash = 0.495 Fatigue =1 Total = 8	No serious adverse effects mentioned.
Stutman et al. (120)	Cephalexin	119	Antibiotic prophylaxis in infants and young children with cystic fibrosis: A randomized controlled trial	60-84 months	Cephalexin 80-100mg/kg/d	Discontinued due to adverse reactions = 15 (authors do not elaborate)	Based on a 50kg patient dosages used by authors were as follows: 4g daily cephalexin to 5g daily cephalexin No serious adverse effects mentioned.
Gower et al. (121)	Cephalexin	25	The use of small doses of cephalexin (125 mg) in the management of recurrent urinary tract infection in women.	12 months	125mg o.d	Persistent diarrhoea = 1 Irritating skin rash = 1	No serious adverse effects mentioned.
Fairley et al. (122)	Cephalexin		Prophylactic long-term cephalexin in recurrent urinary infection.		500mg od		No serious adverse effects mentioned.

Table 7- Data from 4 clinical trials detailing the side effects and uses of cephalexin. Long-term high dose cephalexin regimen is safe. Adverse effects are largely limited to gastrointestinal disturbances and few instances of skin rash, which are uncommon. No serious adverse effects were reported in the examined studies.

(6.2) Second-Line Treatments

Azithromycin

Azithromycin is commonly used for the treatment of Chlamydia. It has been shown that Chlamydia may in fact exist in a quiescent state and result in symptoms indistinguishable from an acute UTI(123). Azithromycin has the ability to concentrate in white blood cells, which target intracellular infection(124). In addition to this mechanism, white blood cells possess a unique ability to migrate from blood vessels into tissue, thus acting as a trafficking agent in delivering azithromycin to other body compartments. This mode of action and delivery may be valuable, where treatment requires access to tissues, which possess hindrance to antibiotic permeability(125). The ability of an antimicrobial agent to penetrate into phagocytic cells is essential for activity against facultative intracellular organisms(126). Despite high intracellular concentration, soft tissue levels may be sub-optimal and high doses are need in order to maximize efficacy and circumvent bacterial resistance(127).

Azithromycin has been widely used in clinical trials for the treatment of diseases as diverse as chronic bacterial prostatitis, chronic chlamydia infection, mycobacterial pneumonia and cystic fibrosis infection prophylaxis(128)(129)(130)(131). Evidence for the uses and safety of azithromycin is presented in **Table 8**, demonstrating that even in instances where azithromycin had been used in very high doses for protracted periods of time no irreversible or life-threatening adverse effects occurred(129). Moreover, these data show that azithromycin may, in fact, be remarkably safe at doses as high as 300mg once daily for 4 months, even in the elderly patients with significant comorbidities. At doses above 300mg once daily patients with comorbidities or reduced metabolic capacity should be closely monitored to avoid unwanted adverse effects. Azithromycin 600mg once daily for 4 months resulted in a significant number of gastrointestinal adverse effects in the elderly patient population with pneumonia.(129). Hearing disturbances were also reported, however five patients had these prior to treatment. There was one questionable instance of a serious adverse effect (liver enzyme derangement). Lower doses of azithromycin, such as 300mg once daily or 500mg thrice weekly are a safe and effective alternative. Another study demonstrated that azithromycin is a safe and effective prophylactic treatment at doses 250-500mg thrice weekly for 6 months(130).

Brown and Colleagues: *Brown et al.* used very high doses of azithromycin 600mg once daily for 4 months to treat mycobacterial pneumonia in 39 elderly patients, with a mean age of 66 years. 33 patients experienced an adverse event, of which most prominent was gastrointestinal disturbance. Hearing disturbance was reported by 10 patients, of which 5 had hearing impairment prior to azithromycin treatment. 2 patients had liver enzyme abnormalities. One of these patients died of respiratory failure. The biopsy confirmed mild fibrotic changes in the liver, which were NOT the cause of death. 20 patients required dose reduction mainly due to GI

adverse effects. Most adverse events reported by *Brown et al.* resolved at doses of 300mg once daily(129).

It is worth noting that *Brown et al.* study recruited elderly patients with a significant comorbidity, namely pneumonia. Mild and moderate side effects were common at higher azithromycin doses. There were few side effects at a smaller dose of 300mg once daily.

Skerk and Colleagues: Skerk et al. treated 127 male patients with azithromycin in two clinical trials. The first trial used doses of 500mg od for 3 days, then thrice weekly for 3 weeks and the second trial used a single weekly dose of 1000mg for 4 weeks. No serious adverse effects were reported in either trial. Of note, 3 patients altogether had mildly elevated serum transaminases, which returned to normal within a week of treatment discontinuation(128)(131).

Saiman and Colleagues: Saiman et al. treated 87 patients with cystic fibrosis with azithromycin 250/500mg thrice weekly for 6 months. Among the adverse events reported, only nausea, diarrhoea and wheezing were found to be statistically different between azithromycin and placebo groups. Nausea occurred in 17% more participants in the azithromycin group, diarrhoea in 15% more and wheezing in 13% more. The majority of adverse events were described as mild or moderate. No severe adverse effects were reported(130).

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Author	Antibiotic	Patients	Design	Duration	Dose	Adverse effects	Comments
Skerk et al. (131)	Azithromycin	45	Randomized comparative study of azithromycin vs. ciprofloxacin for chronic bacterial prostatitis	3 weeks	500mg od for 3 days, then thrice weekly	Nausea = 1 Abnormal Liver Test = 1	Serum transaminases were elevated by less than 3 times of the upper limit and returned to normal on discontinuation after 2 weeks, this does not fit the definition of a serious adverse event set out by this review. No serious adverse effects mentioned.
Skerk et al. (128)	Azithromycin	82	Randomized comparative study of azithromycin vs. doxycylcine for chronic bacterial prostatitis	4 weeks	1000mg once weekly	Abnormal Liver Tests = 2	Abnormal liver tests below 3x upper limit detected in two patients. Levels returned back to normal after 1 week of discontinuation, this does not fit the definition of a serious adverse event set out by this review. No serious adverse effects mentioned.
Brown et al. (129)	Azithromycin	39	Comparative study of adverse events in patients receiving high dose azithromycin with Mycobacterial lung disease	4 months	600 mg o.d	Gastrointestinal = 32 Hearing Impairment = 10 Liver Test Abnormalities = 2 Any adverse event = 33	Mean age of patients enrolled in this study is 66 years. Patients had a significant comorbidity – pulmonary infection with mycobacterium. Out of the 10 patients who complained of hearing impairment 5 had hearing impairment before therapy. One of the patients with liver enzyme abnormalities died of respiratory failure. The biopsy showed minimal fibrotic changes in the liver. Closer analysis revealed that these changes were NOT the cause of the patient's death. Another patient was treated with clarithromycin before azithromycin. 20 patients required dose reduction mainly due to GI adverse effects. Most adverse events reported by Brown et al. resolved at doses of 300mg. od. **This signifies one unconfirmed instance of a serious adverse effect.**
	Azithromycin	20	Comparative study of adverse events in patients receiving high dose azithromycin with Mycobacterial lung disease	4 months	300mg o.d		With discontinuation of 600mg therapy and institution of 300-mg daily dose, patients were able to tolerate the antibiotic, without return of the dose-limiting adverse events.
Saiman et al. (130)	Azithromycin	87	Randomized double blind placebo controlled trial of azithromycin in Cystic Fibrosis patients	6 months	250/500 mg thrice weekly	Nausea occurred in 17% more participants in the azithromycin group, diarrhoea in 15% more and wheezing in 13% more.	Among the adverse events reported, only nausea, diarrhoea and wheezing were found to be statistically different between azithromycin and placebo groups. The majority of adverse events were described as mild or moderate. There were no statistically significant differences in laboratory abnormalities between azithromycin and placebo groups

Table 8- Data from 4 clinical trials detailing side effects and uses of azithromycin. Long-term high dose azithromycin regimen is safe. Side effects become more pronounced at

doses above 300mg od, especially in the elderly population. Lowering the dose of azithromycin reverses adverse effects. Gastrointestinal upsets are common. No organ damage from the use of azithromycin was reported in the examined trial.

Doxycycline

Doxycycline belongs to the class of antibiotics known as tetracyclines. Tetracyclines are known for their ability to penetrate the cells and exhibit activity against intracellular bacteria such as chlamydia, rickettsia, mycoplasma and legionella(132)(133). Traditionally, tetracyclines were praised for good activity against streptococcal, staphylococcal and gram-negative infections, such as *E.coli*. At present, there is quite a lot of resistance to doxycycline amongst *E.coli*, which makes treatment more difficult(134).

Tetracyclines should not be given to children or pregnant women, as they have the ability to accumulate in bone tissue(135). One of their most notorious side effects is photosensitive rash. In general, however, doxycycline is a safe and effective antibiotic. It has been used in the long-term treatment of chronic bacterial prostatitis, melioidosis, Q-fever endocarditis and Lyme disease(128)(136)(137)(138)(139). Numerous trials presented in **Table 9** below demonstrate that its adverse effects are largely limited to mild and moderate reactions. We can conclude that doxycycline is a safe and effective agent for the treatment of recurrent urinary tract infections.

Skerk and Colleagues**:** Skerk et al. treated 43 patients with doxycycline 100mg twice daily for 28 days. Five patients reported gastrointestinal side effects, which were classified as mild. No serious adverse effects were reported(128).

Chaowagul and Colleagues**:** Chaowagul et al. treated 58 patients with doxycycline 100mg twice daily for 12-20 weeks. No serious adverse effects were reported. Chaowagul et al. treated another group of 58 patients with a cocktail of chloramphenicol, doxycycline and co-trimoxazole. This group demonstrated 2 more incidents of vomiting and one more instance of photosensitivity, although no serious adverse effects were reported(136)(137).

Cameron and Colleagues**:** Published a review of evidence regarding numerous aspects of treatment for Lyme disease. The authors concluded that long-term treatment of persistent symptoms of Lyme disease with doxycycline is warranted, despite conflicting evidence of efficacy, if the patients wish to undergo such treatment. Cameron states: "t*he risk–benefit assessment needs to be done on an individualized basis, taking into account the severity of an individual's persistent disease, their responsiveness to treatment, their ability to tolerate side effects associated with additional and potentially long-term treatment as well as their willingness to accept the risk associated with antibiotic treatment"*(138).

Author	Antibiotic	Patients	Design	Duration	Dose	Adverse effects	Comments
Skerk et al. (128)	Doxycycline	43	Randomized comparative study of azithromycin vs. doxycycline for chronic bacterial prostatitis	28 days	100mg bd	Gastrointestinal = 5	The authors refer to nausea, vomiting and abdominal pain as gastrointestinal adverse effects. No serious adverse effects mentioned.
Chaowagul et al. (136)	Doxycycline	58	A randomized comparison of chloramphenicol, trimethoprim-sulfamethoxazole, and doxycycline with doxycycline alone as maintenance therapy for melioidosis.	12-20 weeks	Doxycycline 4 mg/kg/d	Vomiting = 1 Nausea = 3 Abdominal Discomfort = 3 Photosensitivity = 3 No serious AE	Based on a 50kg patient dosages used by authors were as follows: 100mg doxy. bd There were no serious adverse effects.
Rolain et al. (139)	Doxycycline	24	Correlation between Serum Doxycycline Concentrations and Serologic Evolution in Patients with *Coxiella burnetii* Endocarditis (Q-fever)	12 months	Hydroxychloroquine 600mg/d Doxycyline 200mg/d	Authors mention that doxycycline can cause various adverse effects, such as epigastric burning, nausea, vomiting, or hyperpigmentation of the skin after exposure to the sun, No serious adverse effects mentioned.	Authors mention that higher doses (400 mg) may be justified in the treatment of some cases of Q fever endocarditis, especially for patients who are infected with strains with higher resistance against doxycycline. Yet another study that supports protacted high dose antibiotic use. Everyone completed treatment and no patients withdrew due to adverse effects.
Cameron et al. (138)	Doxycycline	221	A review of evidence regarding Lyme disease treatment based on 4 randomized controlled trials by Klempner et al. Krupp et al. Fallon et al.	2 months	Doxycycline 200mg/d IV ceftriaxone 2g.d	60 days of oral doxycycline therapy was not associated with any significant adverse event in the Klempner study. IV ceftriaxone therapy was associated with: Allergic reactions = 6 Anaphylaxis = 1 IV line events = 7	Authors comments: "t*he risk– benefit assessment needs to be done on an individualized basis, taking into account the severity of an individual's persistent disease, their responsiveness to treatment, their ability to tolerate side effects associated with additional and potentially long-term treatment as well as their willingness to accept the risk associated with antibiotic treatment*"p1122

Table 9- Data from 4 clinical trials detailing side effects and uses of doxycycline. Long-term high dose doxycycline regimen is safe. Side-effects are largely limited to gastrointestinal disturbances and very occasional instances of photosensitivity. No serious or life-threatening adverse effects were reported in the examined trials.

Co-Amoxiclav

Co-amoxiclav is a combination of amoxicillin with clavulanic acid. The latter is a chemical compound developed to circumvent resistance to amoxicillin demonstrated in numerous bacteria, including E.Coli(140)(141). Amoxicillin belongs to a beta-lactam class of antibiotic and thus shares their mechanism of action and related side effects(142). An archetypal beta-lactam antibiotic is penicillin. It can be argued, that some physiochemical properties of penicillin may be extrapolated to amoxicillin(143). Beta-lactams are a remarkably safe class of antibiotic medicines. They have relatively poor tissue permeability and are known for gastrointestinal and skin-related hypersensitivity type side effects(142). Nonetheless, numerous studies demonstrate their safety when used in the long-term, even at high doses(144)(145). 14% of E.coli isolates are resistant to co-amoxiclav(94). Evidence for the uses and safety of beta-lactams is presented in **Table 9** below.

Beta-lactams have been demonstrated to be effective at targeting biofilms. However, penicillin and structurally related amoxicillin are not good at crossing cell membranes and accumulating in cells(92)(93)(124). Thus high doses are required to reach effective intracellular concentrations.

The safety of treatment with protracted courses of co-amoxiclav at high doses has been repeatedly demonstrated in numerous clinical trials. Notably, by Rajchanuvong et al. who used co-amoxiclav to treat meliodosis patients for 20 weeks(144). The safety of other beta-lactams is known from long-term studies looking at immunosuppressed children, who take penicillin prophylactically in moderate doses for indefinite periods of time(145). In general, beta-lactams are a safe and effective class of antibiotics for many infections and co-amoxiclav is no exception. From the aforementioned trials, which look at co-amoxiclav and penicillin we can deduce that the most frequent side effects seen with this class are gastrointestinal disturbances.

Rajchanuvong and Colleagues: Rajchanuvong et al. treated 49 of his patients with high dose co-amoxiclav for 20 weeks. Only a few mild adverse effects were reported and all reached full resolution on treatment discontinuation. This is a remarkable safety profile, in light of the fact that 29 patients in this study had other comorbidities, including renal disease and diabetes mellitus(144).

Hirst and Colelagues: Conducted a Cochrane review into prophylactic use of penicillin in children with sickle cell anaemia. This review looked at 857 children on 125-250mg twice daily indefinite penicillin prophylaxis of at least 24 months duration. No significant adverse effects were reported(145).

Summary: Although penicillin itself is not used in the protocol this study illustrates instances, in which exception circumstances would warrant long-term antibiotic use.

Author	Antibiotic	Patients	Design	Duration	Dose	Adverse effects	Comments
Rajchanuvong et al. (144)	Co-amoxiclav	49	An open randomized comparison of co-amoxiclav vs. combination of chloramphenicol, doxycycline and co-trimoxazole in long-term treatment of melioidosis.	20 weeks	Co-amoxiclav 30/15mg/kg/d Amoxicillin 30mg/kg/d QDS	Abdominal Discomfort = 3 Rash = 1 Liver Tests Abnormalities = 1	Based on a 50kg patient dosages used by authors were as follows: 750mg amoxicillin qds 187.5mg clavulanic acid qds This is equivalent to 3g amoxicillin/24hrs, which is double than the maximum dose advocated by JML in the protocol. Rash resolved. Liver Test Abnormalities were increased serum bilirubin, which resolved after 6 weeks, thus this adverse effect can be classified as non-serious using the definition of this review. Only 5 adverse effects prompted medication change. 29 patients had other underlying disease likely exaggerating adverse effects data (i.e renal, diabetes)
Hirst et al. (145)	Penicillin	857	Cochrane review of prophylactic penicillin in children with Sickle Cell looking at 3 randomized placebo-controlled trials	> 24 months	Penicillin 125mg bd-250mg bd.	Trial by John et al. Found no adverse events in the penicillin group. In the PROPS trial it is stated that the penicillin was well-tolerated and no confirmed allergic reactions occurred (PROPS 1986). In the PROPS II trial there were three recorded incidences of nausea and vomiting (one in the placebo group).	Amoxicillin belongs to the same class of antibiotics known as beta-lactams. Despite this adverse effect profile may differ. This evidence was included to demonstrate that INDEFINITE use of long-term antibiotics is advocated in diseases such as sickle cell.

Table 9.- Data from 2 clinical trials detailing side effects and uses of beta-lactams. Long-term high dose co-amoxiclav regimen is safe. Side-effects are largely limited to gastrointestinal disturbances. Allergic reactions and rash may occur less commonly. Liver test abnormalities may rarely occur. No serious or life-threatening adverse effects were reported in the examined trials.

(6.3) Third Line Treatments

Fosfomycin

Is an old antibiotic used a single mega-dose in the treatment of urinary tract infections. First discovered in 1969, it has been shown to posses good activity against more than 90% of strains of *E. coli, Citrobacter diversus, C. freundii, Klebsiella oxytoca, Klebsiella pneumoniae, Enterobacter cloacae, Serratia marcescens, Proteus mirabilis, P. vulgaris, Providencia rettgeri, Pseudomonas aeruginosa, E. faecalis,* and *E. faecium*(146)(147). Resistance to this drug is remarkably uncommon. Fosfomycin is actively taken up into cells thus making it effective at killing intracellular bacteria(148). 200 mg/liter, fosfomycin was able to kill staphylococci surviving within white-blood cell compartments(110). This pattern of activity is reinforced by unprecedented safety track record, with adverse effects data collected for over 40 years. Some of these data are outlined below and summarised in **Table 10.** ***Evidence Summary:*** From the aforementioned evidence it is possible to deduce that fosfomycin is a safe antibiotic. This evidence comprises a review of over 35,481 patients(149). There was only one instance of *clostridium difficile* infection, which could be attributed to the drug.

Falagas, Rudenko and Mayama and Colleagues: A systematic review and a meta-analysis examining the use of fosfomycin in acute urinary tract infections conducted by Falagas et al. looked at 27 randomised controlled trials and concluded that fosmocyin is a safe and effective antibiotic in treating urinary tract infections(150). As mentioned previously systematic reviews are the gold standard of clinical evidence. A randomised placebo controlled trial by Rudenko et al. demonstrated that 10 daily 3 g fosfomycin prophylaxis is effective at reducing the rate and recurrence of urinary tract infections(151). The same research team concluded that fosfomycin is safe and only reported 1 adverse effect. Over the course of the drug's existence which spans over some 45 years only minor, self-limiting adverse effects were observed: rash, headache, nausea, rhinitis, vaginitis etc. In Japan, only one case of pseudomembranous colitis was noted in a post-marketing study involving 35,481 patients over a 6-year period as reported by Mayama et al(149).

Author	Antibiotic	Patients	Design	Duration	Dose	Adverse effects	Comments
Falagas et al. (150)	Fosfomycin	1428	Fosfomycin versus other antibiotics for the treatment of cystitis: a meta-analysis of randomized controlled trials – systematic review and meta analysis	Variable short-term (2-7 days)	Variable regimen	None detailed (see comments)	No study withdrawals due to adverse events were observed either in the fosfomycin or comparator group in 11 of the 13 studies (involving a total of 1428 patients)
Rudenko al. (151)	Fosfomycin	166	Prevention of recurrent lower urinary tract infections by long-term administration of fosfomycin trometamol. Double blind, randomized, parallel group, placebo controlled study.	6 months	One 3g sachet every 10 days	Rash = 1 No other adverse effects	Only 1 adverse reaction possibly treatment related, i.e. an allergic skin reaction, was reported in both groups (drug and placebo)
Mayama et al. (149)	Fosfomycin	35,481	Analysis of oral fosfomycin calcium (Fosmicin) side-effects after marketing.	72 months	Variable dose and duration	Pseudomembranous colitis = 1 (c.difficile infection) Melaena = 1 (white stool) Other side effects were not considered serious or life-threatening: "diarrhea, nausea, abdominal pain, anorexia, eruption and increased serum transaminase were frequent"	There were no withdrawals from the study because of adverse events or for any other reason. As adverse events, 2 cases of deep venous thrombosis were recorded in the ciprofloxacin group and 1 in the placebo group.

Table 10- Data from 2 clinical trials and 1 post-marketing study detailing side effects and uses of fosfomycin. Long-term fosfomycin regimen is safe. Side-effects are largely limited to gastrointestinal disturbances. Serious adverse effects such as C.difficile infections are extremely uncommon (1/35,481). Liver test abnormalities may rarely occur. One serious adverse effect was reported in the examined studies.

Pivmecillinam

Pivmecillinam is a prodrug, which is converted to mecillinam - its active form, in the body. While mecillinam has to be administered intravenously pivmecillinam can be taken by mouth(152). Similarly to co-amoxiclav, it belongs to a beta-lactam class of antibiotics and targets bacterial cell wall for destruction, thus killing the bacteria. It has a broad activity against many microorganisms, including most gram-negative bacteria and E.coli is no exception. Notably, resistance to pivmecillinam has remained low since its introduction, even amongst some of the most resilient strains of E.coli(153). Overall, E.coli are show a 95.2% susceptibility to pivmecillinam(8). Evidence for the safety of pivmecillinam is presented in **Table 11** below. We can conclude that Pivmicillinam has a good safety profile, which is comparable to that of many other beta-lactams.

Author	Antibiotic	Patients	Design	Duration	Dose	Adverse effects	Comments
Bint et al. (154)	Pivmecillinam	49	A Comparative Trial of Pivmecillinam and Ampicillin in Bacteriuria of Pregnancy	6 weeks	400 mg qds	Vomiting = 13 Diarrhoea = 1 Headache = 4 Indigestion = 1 Epigastric fullness = 1	No significant effects on liver function were found. Study was looking at **pregnant** women.
Sanders et al. (155)	Pivmecillinam	38	Pivmecillinam for bacteriuria in pregnancy	3 months	100mg every other day	Withdrawal due to nausea and vomiting = 1 Withdrawal due to diarrhoea = 1	Study was looking at **pregnant** women.
Jodal et al. (156)	Pivmecillinam	20	Pivmecillinam in long-term prophylaxis to girls with recurrent urinary tract infection.	228 months	5-10mg/kg/d	One girl aged 16 years complained of vaginal discharge and discontinued treatment after 3 weeks. No other side-effects were recorded. Thus, the tolerance of pivmecillinam was classified as excellent in the remaining 19 children.	Based on a 50kg patient dosages used by authors were as follows: 500mg pivmecillinam od Authors concluded: "Thus pivmecillinam offered effective protection against recurrent urinary tract infections, and did not tend to select resistant enterobacteria in the bowel, but allowed resistant enterococci to cause a few symptomatic infections."
Carlsen et al. (109)	Pivmecillinam	33	Comparison of long-term, low-dose pivmecillinam and nitrofurantoin in the control of recurrent urinary tract infection in children. An open, randomized, cross-over study.	6-10 months	100mg od and 100mg bd depending on age	Loss of appetite = 1 Indigestion = 2 Loose stools = 1 Tiredness = 2	No serious adverse effects.

Table 11- Data from 4 clinical trials detailing side effects and uses of fosfomycin. Long-term pivmecillinam regimen is safe. Side-effects are largely limited to gastrointestinal disturbances. No serious or life-threatening adverse effects were reported in the examined trials.

(6.4) Fourth-Line Treatments

Ciprofloxacin

Ciprofloxacin belongs to a class of antibiotics known as quinolones. In general, quinolones have good cellular penetrance in phagocytic cells but plasma levels required need to be high(96). Ciprofloxacin is capable of achieving high intracellular concentration but despite this, short-term administration of ciprofloxacin has not achieved complete eradication of intracellular bacterial communities within epithelial cells of the bladder(124). Moreover, resistance to ciprofloxacin in the United Kingdom has risen by some 15% in the past 6 years(94).

The relative safety of this antibiotic has been demonstrated in numerous clinical trials, where it has been used in treatment of chronic bacterial prostatitis, reactive arthritis, ulcerative colitis and osteomyelitis(131)(157)(158)(159). In the latter very high doses were employed for protracted periods of time with very few adverse effects(159). Main data extracted from the evidence for long-term use of

ciprofloxacin and the associated adverse effects are outlined in **Table 12** below. Ciprofloxacin is a safe antibiotic. The studies conducted with high doses of ciprofloxacin and with protracted periods of treatment indicate that side effects are largely limited to gastrointestinal disturbances, occasional incidents of photosensitivity and constitutional symptoms.

Norrby and Colleagues: Used high doses of Ciprofloxacin to treat osteomyelitis. Doses between 500mg and 1500mg were employed twice daily for 17 months. The authors concluded that safety of such regime was comparable to that reported in shorter treatment durations despite long-term high dose treatment. There were 3 instances of photosensitivity and 1 instance of renal function abnormality, which resolved on discontinuation(159).

Author	Antibiotic	Patients	Design	Duration	Dose	Adverse effects	Comments
Skerk et al. (131)	Ciprofloxacin	44	Randomized comparative study of azithromycin vs. ciprofloxacin for chronic bacterial prostatitis	20 days	500mg bd	None reported	No side effects were reported for ciprofloxacin by Skerk et al. No serious adverse effects mentioned.
Sieper et al. (157)	Ciprofloxacin	48	A Three-Month, Multicenter, Double-Blind, Randomized, Placebo-Controlled Study of doxycycline in Reactive Arthritis	3 months	500mg bd	Mild abdominal symptoms = 10 Mild neurologic symptoms = 8 Nonspecific symptoms = 2 Granulocytopenia = 1 Other symptoms = 7	Authors: "Surprisingly few side effects were observed during the 3-month period of ciprofloxacin treatment compared with placebo"
Turunen et al. (158)	Ciprofloxacin	38	Long-term treatment of ulcerative colitis with ciprofloxacin: A prospective, double-blind, placebo-controlled study	6 months	500-750mg bd	Deep venous thrombosis = 2 (the placebo group also had 1 incidence of deep venous thrombosis)	There were no withdrawals from the study because of adverse events or for any other reason. As adverse events, 2 cases of deep venous thrombosis were recorded in the ciprofloxacin group and 1 in the placebo group.
Norrby et al. (159)	Ciprofloxacin	182	Evidence review of ciprofloxacin in osteomyelitis. Title: "Ciprofloxacin in the treatment of acute and chronic osteomyelitis: a review".	17 months	500-1500mg bd Commonly 750mg bd	Photosensitivity = 3 Renal Function Abnormality = 1 (reversible, thus does not constitute a serious adverse effect)	Authors: "Despite very long treatment times (up to 476 days), the **safety of ciprofloxacin seemed comparable to that reported with shorter treatment times and lower doses**."

Table 12- Data from 3 clinical trials and 1 systematic review detailing side effects and uses of ciprofloxacin**.** Long-term high dose ciprofloxacin regime is safe. Side-effects are largely limited to gastrointestinal disturbances, occasional incidents of photosensitivity and constitutional symptoms. One reversible adverse effect was reported in a patient with osteomyelitis treated with high-dose ciprofloxacin for 17 months, which could otherwise be classified as serious.

(6.5) Fifth Line Treatments

Meropenem

Meropenem belongs to a beta-lactam class of antibiotics with a very broad spectrum of activity. Similarly to co-amoxiclav and pivmecillinam it kills bacteria by targeting their cell wall.

It has the capacity to withstand many drug-resistant bacteria, specifically those that are capable of producing extended spectrum beta-lactamase – a substance which helps resistant strains escape destruction by many other antibiotics(160). Meropenem is the agent of choice for empiric treatment of serious infections caused by suspected gram-negative pathogens, and for directed treatment of multidrug-resistant bacteria(161)(162). Intravenous administration and high potency mark this agent as the last treatment option of severe recalcitrant cystitis. Nonetheless, belonging to a beta-lactam class this antibiotic is remarkably safe.

Linden and Norrby and Colleagues:A large systematic review conducted by Linden et al. found merapenem to possess an excellent safety profile. Linden looked at the incidence of adverse effects in 6,154 patients who received meropenem treatment and found that the most common adverse events were diarrhoea (2.5%), rash (1.4%) and nausea/vomiting (1.2%). He also found that no adverse event occurred in more than 3% of patient exposures to meropenem. This clearly indicates a low frequency of adverse events as well as excellent gastrointestinal tolerability profile(163). This safety analysis, together with Norrby's review of over 4800 patients are summarised in **Table 13** below(159). Despite its potency meropenem is amongst some of the safest antibiotics currently used in clinical practice. Its broad spectrum of activity makes it a promising treatments for patients with multidrug resistant microorganisms.

Author	Antibiotic	Patients	Design	Duration	Dose	Adverse effects	Comments
Linden et al. (163)	Meropenem	6154	Safety profile of meropenem: an updated review of over 6,000 patients treated with meropenem.	Variable	Variable	Diarrgoea = 2.5% Rash = 1.4% Nausea/vomiting = 1.2% Overall = <3% Seizures = 0.07%	Only 4 patients in over 6100 experienced treatment related seizures.
Norrby et al. (159)	Meropenemm	4872	Safety profile of meropenem: a review of nearly 5,000 patients treated with meropenem.	Variable	500mg-1g I.V 8	Diarrhoea = 2.3% Rash = 1.4% Nausea/vomiting = 1.4% Injection site inflammation = 1.1% Thrombocytosis = 1.6% Increased hepatic enzymes = 1.5-4.3%	Authors: "In meropenem-treated patients with meningitis, the incidence of seizures was low and none were drug related"

Table 13- Data from 2 clinical reviews detailing side effects and uses of meropenem across 10,000 patients. Meropenem is a safe and effective drug. Side-effects are largely limited to gastrointestinal disturbances.

Gentamicin

Gentamicin belongs to an aminoglycoside class of antibiotics. It acts by preventing bacteria from making protein for growth and replication, thus halting their development and resulting in their imminent death. Gentamicin has a rapid onset of action and is administered intravenously to achieve high blood concentrations and high concentrations at sites of infection. It has a capacity to enter bacterial and other cells via specific gateways(124)(93)(99). Importantly, some bacteria have the ability to shut those gateways, preventing gentamicin from acting on them(164)(165). It has very little activity against anaerobic bacteria (i.e those that do not required oxygen for respiration).

Gentamicin has long been associated with concerns over ototoxicity, nephrotoxicity and less often neuromuscular toxicity. Patient factors play a very important role in determining who is likely to react poorly to gentamicin treatment. The most important factors are pre-existing disease, severity of illness, co-administered drugs and genetic susceptibility(166). Prolonged therapy has been shown to be an independent risk factor for toxicity(167)(168). Monitoring for toxicity can be through blood tests for organ function, active bedside assessment and passive reporting by the patient. There is no definitive evidence to inform optimal techniques for monitoring of toxicity(167). Nephrotoxicity and ototoxicity can be as high as 15% in those receiving gentamicin twice daily(168). This figure is significantly lower on a once daily regimen and was found to be 0% in one study(169). Rybak et al. also mentioned that concomitant vancomycin use was a high predictor for toxicity(169).

Gentamicin poses a pronounced risk of ototoxicity and nephrotoxicity when used twice daily in therapeutic doses. When used once daily, these risks may decrease significantly. Nonetheless, continuous monitoring by assessing patients organ function using blood tests, assessing patients clinical status by clinical examination or assessing patient status through passive reporting of toxicity symptoms should be performed. No one method of monitoring is superior to another.

(6.6) Non-Antibiotic Agents

Methenamine Hippurate

Methenamine hippurate is not classified as an antibiotic. It is more similar to a urinary antiseptic and has been widely used in treatment of recurrent urinary tract infections. It has a very narrow side effect profile and is widely regarded as a safe medicine. In the acidic pH of the urine it has the ability to breakdown it its constituents: formaldehyde and ammonia(170). Formaldehyde is a bactericidal substance. It is commonly co-administered with large doses of Vitamin C to ensure adequate acidification of urine in order to maintain sufficient formaldehyde levels. Notably, because formaldehyde is fundamentally toxic to exposed bacterial cells at a physicochemical level it does not produce any resistance. It is highly active against bacteria, which are shed into the urine from the lining of the bladder. Unfortunately, it has no ability to affect bacteria, which are protected by epithelial cells or biofilms. Evidence detailing the uses and safety of methenamine hippurate is outlined in

Table 14 below. Methenamine hippurate may be useful at reducing the load of live bacteria in the bladder in instances where shedding of intracellular bacteria or microorganisms from biofilms occurs. It is associated with a very low risk of side effects all of which can be described as non serious adverse effects

Author	Antibiotic	Patients	Design	Duration	Dose	Adverse effects	Comments
Cronberg et al. (171)	Methenamine Hippurate	21	Prevention of recurrent acute cystitis by methenamine hippurate:doubleblindcontrolledcrossover longterm study	12 months	Methenamine hippurate 1g bd	None reported.	Authors: methenamine hippurate is well tolerated, is effective, and fails to produce cross resistance to conventional antibiotics it seems to be a suitable prophylactic agent against recurrent acute cystitis in women.
Kasanen et al. (108)	Methenamine Hippurate	73	Comparison of the Effect of Placebo, Methenamine Hippurate, Nitrofurantoin and Trimethoprim Alone	12 months	Methenmaine hippurat 1g od	Rash = 1 Nausea = 2	No serious adverse effects reported.
Lee et al. (172)	Methenamine Hippurate	2032	Methenamine hippurate for preventing urinary tract infections. Systematic review and meta-analysis.	1 week	Variable	Nausea = 12 Constipation = 1 Rash = 3 Diarrhoea = 1 Sore throat = 1 Bladder stinging = 1	The rate of adverse events was low, but poorly described.

Table 14- Data from 2 clinical trials and 1 systematic review detailing side effects and uses of methenamine hippurate**.** Methenamine hippurate is a safe and effective drug. Side-effects, where present are largely limited to gastrointestinal disturbances.

(6.7) Antibiotics combinations and their safety

Polypharmacy is undoubtedly associated with increased risk of drug interactions and potential adverse effects. Due to the unique nature of the protocol it is difficult to quote studies, which used the same combinations of antibiotics. However, there are a few notable examples where combinations of potentially more promiscuous agents have been used successfully, without serious adverse effects. Multiple long-term antibiotic combinations are effective at treating melioidosos with a wider adverse effect profile compared to monotherapy but no reported life-threatening or serious adverse effects(137) (144).

Rajchanuvong and Colleagues: This team treated melioidosis (*Burkholderia pseudomallei* infection) with a 4 drug antibiotic cocktail of chloramphenicol, doxycycline and co-trimoxazole (trimethoprim and sulphamethoxazole). In this treatment arm nine patients reported nausea, there was one instance of resolved photosensitivity and one instance of pruritus. Fifteen patients were changed to a co-amoxiclav regimen but no serious adverse effects were reported, despite the fact that 24 patients had other comorbidities, including renal disease and diabetes mellitus(144).

Chaowagul and Colleagues: Chaowagul et al. treated 180 patients with two different antibiotic combinations, one with doxycycline and co-trimoxazole and one with chloramphenicol and co-trimoxazole for 12-20 weeks. No serious or life-threatening adverse effects were reported in these groups. Total number of adverse effects in the first group was 20, while the second group had 37 instances(137).

Author	Antibiotic	Patients	Design	Duration	Dose	Adverse effects	Comments
Rajchanuvong et al. (144)	Antibiotic Cocktail: Chloramphenicol Doxycycline Trimethoprim Sulphamethoxazole (co-trimoxazole)	52	An open randomized comparison of co-amoxiclav vs. combination of chloramphenicol, doxycycline and co-trimoxazole in long-term treatment of melioidosis.	20 weeks	Chloramphenicol: 40/mg/kg QDS Doxycylcine:5mg/kg/d Trimethorpim: 10mg/kg/d Sulphamethoxazole: 50mg/kg/d	Nausea = 9 Photosensitivity = 3 Puritus = 1	Based on a 50kg patient dosages used by authors were as follows: 500mg chloram. qds 100mg doxy. bd 250mg trimet. bd 1.25g SMX bd. Photosensitivity resolved. 15 adverse events prompted change to co-amoxiclav regimen. 24 patients had other underlying disease likely exaggerating adverse effects data (i.e renal, diabetes).
Chaowagul et al. (137)	Cocktail: Chloramphenicol Doxycycline Trimethoprim Sulfamethoxazole (co-trimoxazole)	58	A randomized comparison of chloramphenicol, trimethoprim-sulfamethoxazole, and doxycycline with doxycycline alone as maintenance therapy for melioidosis.	12-20 weeks	Chloramphenicol: 40g/kg/d Doxycycline 4 mg/kg/d Trimethoprim 8mg/kg/d Sulphamethoxazole 40mg/kg/d	Vomiting = 5 Photosensitivity = 4 Skin hyperpigmentation = 1	Based on a 50kg patient dosages used by authors were as follows: 500mg chloram. qds 100mg doxy. bd 200mg trimet. bd 1g SMX bd. There were no serious adverse effects.
Chaowagul et al. (136)	Cocktail I: Trimethoprim Sulfamethoxazole (co-trimoxazole) Doxycycline	89	Open label randomized comparative trial of two antibiotic cocktail regimens for melioidosis	12-20 weeks	Doxycycline 4 mg/kg/d Trimethoprim 8mg/kg/d Sulphamethoxazole 40mg/kg/d	Gastrointestinal = 6 Rash = 8 Photosensitivity = 3 Anaemia = 1 Angular stomatitis = 0 Anorexia = 0 Chest discomfort = 0 Other = 3 Any = 20	Based on a 50kg patient dosages used by authors were as follows: 100mg. doxy. bd 60mg. trimet. bd 800mg SMX bd Gastrointestinal refer to either nausea, vomiting or abdominal pain in isolation or in combination. No serious life-threatening adverse effects reported. The group of patients studied had a significant comorbidity – infection with *Burkholderia pseudomallei* which may have exaggerated adverse effects data. Despite this no serious or life-threatening AEs were reported.
	Cocktail II: Chloramphenicol Trimethoprim Sulfamethoxazole (co-trimoxazole)	91	Open label randomized comparative trial of two antibiotic cocktail regiments for melioidosis	12-20 weeks	Chloramphenicol: 40g/kg/d Doxycycline 4 mg/kg/d Trimethoprim 8mg/kg/d Sulphamethoxazole 40mg/kg/d	Nausea vomiting Abdominal pain = 14 Rash = 9 Photosensitivity =6 Anaemia = 7 Angular stomatitis = 3 Anorexia = 3 Chest discomfort = 1 Other = 4 Any = 37	Based on a 50kg patient dosages used by authors were as follows: 500mg chloram. Qds 100mg. doxy. bd 60mg. trimet. bd 800mg SMX bd No serious life-threatening adverse effects reported. The group of patients studied had a significant comorbidity – infection with *Burkholderia pseudomallei* which may have exaggerated adverse effects data. Despite this no serious or life-threatening AEs were reported.

Table 15.- Evidence detailing the safety of antibiotic combinations in the treatment of melioidosis.

(6.8) Long-term high dose antibiotics in other infections

Leprosy Treatment

Leprosy treatment warrants 24 months of high dose antibiotics. In a study by Shaw et al. no significant adverse effects were reported in patients treated over 24 months(173).

Q-Fever Treatment

Q-Fever may required protracted courses of high dose antibiotics. Rolain et al. looks at efficacy and safety of hydroxychloroquine 600mg and doxycycline 200mg daily, concluding that treatment is both safe and effective over 12 months. Authors mention that doxycycline can cause various adverse effects, such as epigastric burning, nausea, vomiting, or hyperpigmentation of the skin after exposure to the sun but do not report any significant adverse effects(139)(174).

Lyme Disease

Cameron et al. reviewed the use of doxycycline for 2 months among other treatments and concluded that 60 days of oral doxycycline therapy was not associated with any significant adverse event based on the Klempner et al study.

Overall, There is a large body of evidence showing that long course of antibiotics are often used to treat Leprosy, Q-Fever and related complications, such as endocarditis and Lyme disease. These diseases are characterised by persistent and resilient bacterial colonisation, where the organisms can exist in quiescent intracellular reservoirs and cause chronic or recurrent symptoms. Treatment of leprosy is successful and relatively safe in view of the risk-benefit analysis. Long-term protracted use of high dose doxycycline is safe and effective in Q-Fever. The review of long-term doxycycline use in patients suffering from persistent Lyme disease symptoms shows that evidence for the use of long-term high dose antibiotics in this condition is conflicting. Cameron et al. wisely concludes by saying "*he risk– benefit assessment needs to be done on an individualized basis, taking into account the severity of an individual's persistent disease, their responsiveness to treatment, their ability to tolerate side effects associated with additional and potentially long-term treatment as well as their willingness to accept the risk associated with antibiotic treatment*"(138),

Author	Antibiotic	Patients	Design	Duration	Dose	Adverse effects	Comments
Shaw et al. (173)	Regimen A: Rifampicin Clofazimine Acedapsone Dapsone	16	Effectiveness of multidrug therapy in multibacillary leprosy: a long-term follow-up of 34 multibacillary leprosy patients treated with multidrug regimens till skin smear negativity	24 months	600 mg rifampicin 300 mg oclofazimine on 2 consecutive days monthly, 225mg acedapsone bimonthly 100mg dapsone od	All the patients tolerated MDT well and no adverse effect to MDT except clofazimine discolouration) was seen.	JML does NOT use these drugs in the clinic. However, leprosy is yet another example, where long-term 24months antibiotic therapy is required. Despite the drug cocktail and protracted duration of treatment no serious adverse effects were reported.
Wallace et al. (174)	Clarithromycin	14	Clinical trial of clarithromycin for cutaneous (disseminated) infection due to Mycobacterium chelonae.	6 months	Clarirthomycin 500mg bd	Only mild adverse effects were reported. Nausea = 3 Diarrhoea = 1	One patient with nausea was on concomitant amikacin. No abnormalities on blood tests occurred. Liver function tests were normal. NOT used in JML clinic. Illustrates that long-term antibiotics ARE used clinically in other diseases with good safety profiles.
Cameron et al. (138)	Doxycycline	221	A review of evidence regarding Lyme disease treatment based on 4 randomized controlled trials by Klempner et al. Krupp et al. Fallon et al.	2 months	Doxycycline 200mg/d IV ceftriaxone 2g.d	60 days of oral doxycycline therapy was not associated with any significant adverse event in the Klempner study. IV ceftriaxone therapy was associated with: Allergic reactions = 6 Anaphylaxis = 1 IV line events = 7	

Table 16.- Data from 2 clinical trials and 1 systematic review detailing side effects and uses of various long-term antibiotic treatments in Leprosy, Q-Fever and Lyme disease. Methenamine hippurate is a safe and effective drug. Side-effects, where present are largely limited to gastrointestinal disturbances.

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Appendix 1

Professor Malone-Lee Treatment Protocols

DEPUTATION STATEMENT

on behalf of the Patients of the LUTS Clinic, Whittington Health

APPENDIX K

The Treatment of Lower Urinary Tract Symptoms in Professor Malone-Lee's Centre.

13 April 2014

Medical Urology
Hornsey Central Neighbourhood Health Centre
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We treat patients who present with cystitis, so called "interstitial cystitis", bladder pain, pelvic pain, recurrent urinary infection, voiding problems and overactive bladder symptoms. These complaints overlap and sometimes share causes.

A particularly common story starts with an acute urine infection that is treated conventionally but the patient senses that it has not cleared properly. A more assertive antibiotic course is used but still the non-specific feeling of active disease remains. Conventional urine tests prove negative. There then follows a long history of recalcitrant symptoms punctuated by acute attacks, commonly occurring with negative findings in the tests used to seek a cause. With time, the symptoms become tenacious, distressing and disruptive of normal life and family relationships. The negative tests findings result in a diagnosis and treatment impasse.

The most probable current explanation is that patients experience an infection of the bladder that involves parasitisation of the lining, urothelial cells. The affected cells signal their distress and an inflammatory reaction starts. The inflammation irritates the bladder causing frequency urgency and pain. The longer the inflammation persists, the more complex the symptoms. Pain can radiate to different parts of the pelvis, the vagina, legs and loins. Usually, patients describe relentless low-level symptoms punctuated by acute flares and that can be distressing. These outbreaks are interpreted as isolated acute urine infections, but the evidence points to exacerbations of the same untreated disease. A recurring feature of the history is that the patients, convinced of a urine infection, are confounded when their urine tests negative. It is usual for the patient to be exposed to other investigations including blood tests, cystoscopy, bladder biopsy, renal tract imaging and urodynamic studies. Given the pathology, we should expect these investigations to be unhelpful. Some procedures including urethral dilation, cystodistension and bladder instillations are advocated, but these could not remedy the causative infections.

The routine tests used to check for urine infection have been discredited. If they are positive, an infection is very likely. If negative, an infection is not excluded. The evidence implies that the patients' symptoms are accurate in indicating infection.

We use different methods to detect urinary tract infection. These are not as sensitive as we should like but they are better validated and superior to dipsticks and routine urine culture. All tests will be compromised by the dilution effect of a high fluid intake. We use a microscope to examine immediately fresh urine and count the white blood cells and the urothelial cells being excreted in the urine. This has been shown to be the best, if imperfect, of all the tests.

If the correct treatment is instituted, the urinary epithelial and white blood cells counts will fluctuate slowly down to zero. Despite clear urine the infection will still be present so we then use symptoms to guide management. Thus, it is not always necessary to check the urine to assess progress. The symptoms that are all important, no tests are superior.

Our studies incriminate a deep-seated infection by pathogenic microbes that live inside the urothelial cells or are glued to their surface in colonies called biofilms. We suspect that normal people may be similarly affected but with friendly microbes that do no harm. Problems arise when pathogenic bacteria hijack a natural relationship and make mischief. Microbes inside cells or in biofilms are very resistant to immune or antibiotic attack. Some of the affected cells are deep in the tissues. The mechanisms that the bacteria use to defend their territory have evolved over millennia; they are extremely sophisticated and make it difficult to get the infection out. This is nothing unusual; difficult ingrained infections have always existed.

We use antibiotics to treat these infections. In order to get sufficient into the affected tissues we have to use the highest, tolerated doses. Low-dose, once daily regimes seem unreliable. These ingrained infections require long treatment courses.

We shall check that a treatment is correct by looking for improvement. We then stop treatment briefly and look for signs of relapse. That way we validate the antibiotic recipe for individual patients. The infections are commonly mixed and one antibiotic may be insufficient. A second may be added, but it must be endorsed by showing an improved response which reverses when the antibiotic is withheld. This start/stop process is important to validate all treatments. We may have to alter treatment to find a regime that a person can tolerate. The outcome measures used to check progress, are symptoms, change in urinary white blood cell counts, and changes in urinary urothelial cell count. We have new better culture methods but they are not suitable for monitoring treatment.

In summary; if the treatment is effective there will be symptom improvement and the urinary white blood cell and urothelial cell counts will start to fall, although they oscillate on the way down. Eventually the urine clears, but this does not mean that the infection has been eradicated and the symptoms will indicate this. Infection and

inflammation of the bladder can persist for many weeks without urine signals. We have learned this from biopsy studies and from experiments in stopping treatment at different stages of progress.

Urinary antibiotics will kill bacteria that break out of the cells and prevent them from infecting new cells. A full dose, twice daily, to keep levels up over 24-hours, is superior to once daily regimes which allow the disease to escape during the antibiotic trough. It seems, from dose titration studies, that the antibiotics do penetrate the tissues and influence some of the infection. We suspect that dormant infection where the microbes are not dividing is less susceptible.

We have much data from longitudinal treatment studies. These show that the cell-associated infection of the bladder wall subsides gradually. This is associated with slow clearance of the pains, with symptoms clearance lagging significantly behind the urine. Cessation studies, have taught us not to attempt stopping antibiotics until the urine is clear and all symptoms have gone. Despite that caution, some patients relapse rapidly and require longer treatments. We never treat a person without evidence of efficacy from brief treatment start/stop trials.

Contrary to popular expectation, we experience few problems with antibiotic resistance. There are Darwinian reasons for this because bacterial resistance results from evolution. The bacteria divide very slowly so that replication and variation are minimal. The antibiotic doses provide a lethal selection pressure that favours extinction, as opposed to evolution. For resistance to evolve the correct balance of variation, replication and selection must exist. Our approach is designed to subvert those elements. The antibiotics do not affect a person’s immunity.

There is no cancer risk that we know of and cystoscopy is not helpful or desirable. No imaging studies or urodynamic studies have shown evidence of value. Symptom analysis; microscopy of immediately fresh urine; and spun urinary sediment culture have been validated by rigorous studies.

This condition has nothing to do with allergy or diet, other than specific reactions particular to an individual. The nutritionists, herbalists and other complementary and alternative practitioners offer nothing that has survived the scrutiny of evidence. The symptoms are not caused by psychological problems and they are not imagined. Hypnosis and psychoanalysis have failed to provide evidence of efficay.

The value of urethral dilation or bladder dilation is untested and may be harmful. There is solid data showing that infection of the bladder induces the symptoms of hesitancy, reduced stream intermittency and terminal dribbling. This invariably settles with treatment of the underlying infection. The infection causes the voiding problem and not *vice versa*.

The frequent occurrence of mixed infections is important. They explain bizarre symptom changes and unexpected exacerbations on exposure to an antibiotic. The

current antibiotic kills some microbes but other insensitive bugs grow to occupy the vacated space. Usually these opportunistic colonies are harmless but if a pathogen spreads, it will cause symptoms but these may be different because the species is not the same. Since the current antibiotic is effective we maintain it and layer in a second. We have learned that stopping the first antibiotic often results in relapse because it was doing some good.

Once we have established a regime that is not causing side effects but is showing a in symptoms reduction, and the urinary cells are falling, we test the value of the treatment by stopping briefly. If symptoms and signs come back we have confirmed the validity of the regime. We must then continue long-term and use dogged persistence. We rarely manage to achieve a treatment course of less than six months, although we constantly test this limit. The symptoms will be slow to resolve and the urine will clear long before them. Thus, there will come a time when we shall have to rely far more on the symptoms than the urine tests.

This does require a great deal of patience and courage; we know that this is very hard to endure. We must not allow impatience to prompt treatment alterations in vain attempts to speed response.

The urinary tract tissues are quite battered and sore and susceptible to infection. From time to time acute exacerbations or flares may occur because other bugs have taken advantage of the vulnerability of the bladder. Treated promptly these should not cause dismay. They are expected and do not imply a serious threat. We tend to respond to these by increasing the dose of the current regime first, before considering alternative strategies

We do realise that this approach is unusual and contrary to what has been taught. Questioning standard guidelines and tests is unwelcome. We have attracted plenty of criticism and scepticism but we can answer with the evidence from our science. This evidence has been growing steadily for some years. We are not treating our patients speculatively, but by drawing on an empirical evidence set that has been collected during the last 20 years.

Well aware that we should attract criticism, we ensured, through governance and external review, that our science was meticulously careful with all studies repeated a minimum of thrice. Other centres, particularly in the USA and Australia, are now reproducing are results. The antibiotic policies were developed using empirical methods of evolutionary epistemology, developed by John Dewey, Karl Popper, Konrad Lorenz, Donald Campbell, and Stephen Toulmin. We are confident that the science has been rigorous, conscientious and duplicated many times.

We were most conscious of safety during the development of these regimes and remain so. We maintain very close safety monitoring. We see remarkably little antibiotic resistance. Nowadays studies, using advanced cultures that monitor patients during treatment, show that our patients become colonised by microbes that

are more sensitive to antibiotics than those at the start. There are very good Darwinian, reasons for this.

An important concern is C.Diff diarrhoea. We have reviewed 4530 patients who have been treated according to our protocols. There were three cases of C.diff infection; two patients were taking quinolones, and the third doxycycline and Nitrofurantoin. Thus the probability for of occurrence is 0.0007 or 1 in 1510 cases. We have inherited eight patients with previous histories of infection and none have relapsed despite us treating their urinary infection.

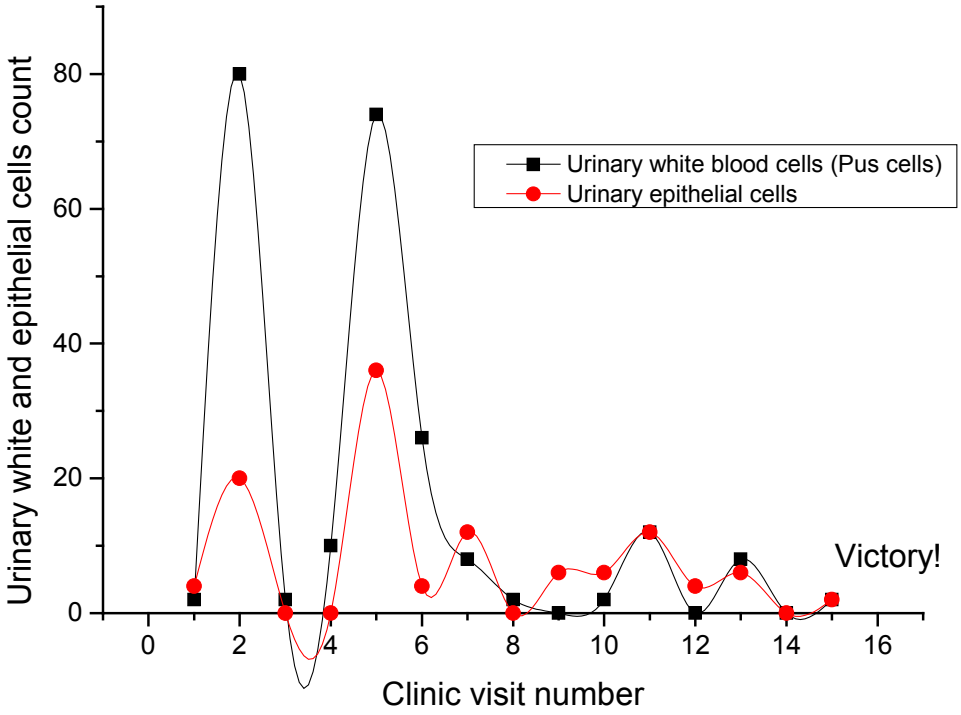
The antibiotics that we use, particularly cephalexin, exhibit the lowest risks for C.diff infection. The recipes that we use have been selected to favour the least toxic antibiotics and it is only in unusual situations that we use high-grade very broad-spectrum modern drugs. Most of our prescriptions are for very old medications that have been around for decades

All of the data that underpin these principles of care are in the public domain. We publish first in the conference abstracts and then follow with the much slower process of publication in the peer-reviewed journals. All of the salient diagnostic and pathophysiological data are in peer-reviewed journals. Clinical treatment outcome and side effects data are being submitted currently.

What should our patients expect?

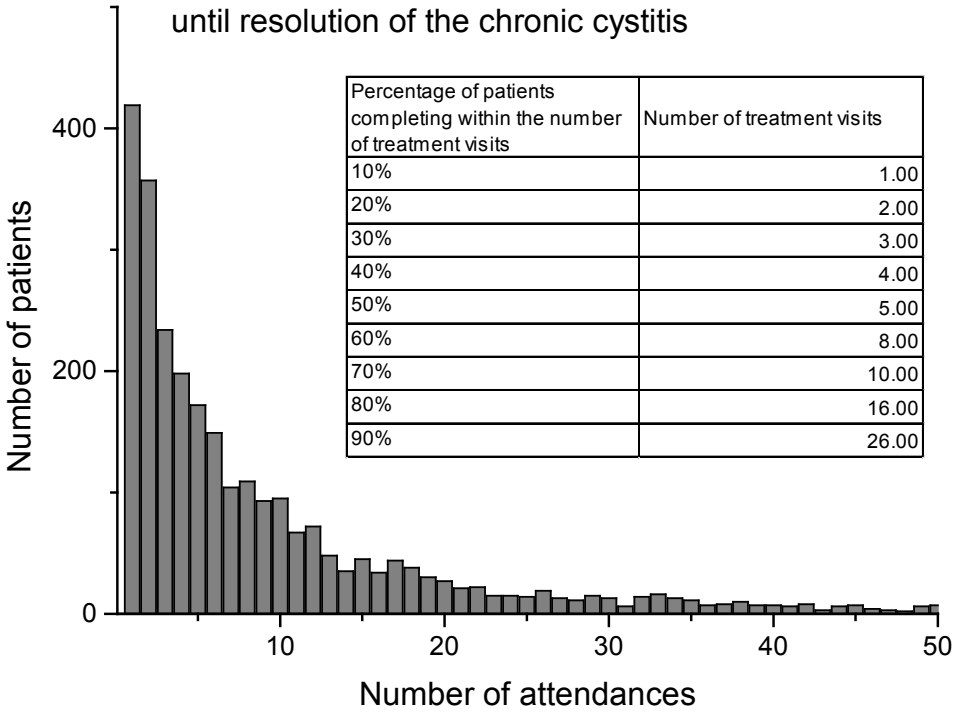
To answer this question I am providing below a graph that was plotted from the data of a patient who has been treated for an unusually difficult problem. As will be explained this is not the norm but it does make an illustrative story/

This graph plots the urinary white cells (black squares) and epithelial cells (red circles) over the course of treatment covered by 16 visits to the clinic.



The patient aged, 42, had suffered undiagnosed chronic urinary infection for two years. She was treated by us with antibiotics over three years (2011 to 2014). The acute flares of decreasing amplitude are well shown. Despite the lower peaks, the symptoms tended to be more severe during the later flares. The intensity of symptoms often prove misleading, being more severe when the inflammation is less. Thus they did do not necessarily imply treatment failure. This patient required 16 visits to the clinic over three years. Only 20% of our patients would take this long; 80% require much less. We are not able to predict how long it will take for an individual patient and the next graph helps to explain why: The graph plots number of visits that patients required to achieve resolution. Thus one follow up visit is the commonest but it only applies to 10%. Half of all patients (50%) require up to five visits.

A frequency distribution of the number of clinic attendances until resolution of the chronic cystitis



Percentage of patients completing within the number of treatment visits	Number of treatment visits
10%	1.00
20%	2.00
30%	3.00
40%	4.00
50%	5.00
60%	8.00
70%	10.00
80%	16.00
90%	26.00

It can be seen that there is much variation in the length of treatment for us to be able to predict an individual case. However, the plot shows that the majority require quite moderate numbers of visits. Half of patients have completed care by five visits. Only 30% require more than ten visits. We emphasise the need for patience and perseverance but for the greater majority there will be a clear end in sight.

These data demonstrate the slow progress that is accomplished when treating these urinary infections. Ceasing antibiotics before the cells have cleared from the urine usually results in relapse. Uninterrupted treatment, with full dose of the effective antibiotic, does not lead to resistance or immune damage. The treatment is controversial but it is effective and nowadays supported by a large scientific evidence set, as well as extensive safety data. It requires patience and dogged persistence. We have yet to discover a quick fix and none have been reported in the literature.

Safety Warning

Because this takes time, and antibiotics are prescribed, contradictory opinions will be offered by others. Some of these opinions will be assertive and dogmatic. We have to take a compassionate account of this pressure.

We reassure that all our methods derive from scientific evidence. We correspond often, with the other centres worldwide working and publishing in this field. There are two university microbiology groups in America and one in Australia. There are two

university neurology centres in the UK. At UCL we collaborate with academic microbiologists, nephrologists, urologists, gynaecologists and obstetricians. We review and criticise each other's work. If alternative methods existed we should know.

This is important because of other management methods and tests that might be proposed: Urodynamics, cystoscopy, urethral dilation, biopsy and hydrodistension of the bladder; may cause a return of the infection to the start. Stopping the antibiotic regime may also cause a serious relapse.

We shall arrange scans when our urine tests, the symptoms and signs indicate that they are necessary. We look for indicators of kidney damage and cancer every time that we examine the urine. We shall never test routinely to "rule things out" because it is bad medicine.

Thus, if other clinicians, private or NHS, alter the regime, or introduce instruments into the bladder, they must accept full responsibility for future treatment through to resolution. Professor Malone-Lee is always available to speak to other clinicians and GPs and all his patients know how to contact him.

James Malone-Lee MD FRCP

April 2014

DEPUTATION STATEMENT

on behalf of the Patients of the LUTS Clinic, Whittington Health

APPENDIX L

DRUG & THERAPEUTICS COMMITTEE

Highgate Hill
London N19 5NF

Professor James Malone-Lee
Consultant Physician
Whittington Hospital

30 June, 2013

Dear James,

Re: Antibiotic treatment of chronic urinary tract infection

In their recent letter (attached), which we have already discussed, Islington CCG raised valid concerns about the prescription of antibiotics for chronic urinary tract infection outside of current local and national guidelines.

I understand that this practice is the logical development of a research programme that yours and other groups are pursuing with regard to intracellular infections within the transitional cells of the bladder wall. The problem of chronic lower urinary tract symptoms which are potentially of an infectious nature is an important area of research and your line of enquiry potentially very valuable. However it is important to bear in mind that this potential pathology has not yet reached a wide level of acceptance and that therefore patients may be exposed to a degree of harm because of the prolonged prescription of antimicrobial agents which include those of both a low and high therapeutic index.

To make the management of this small but important group of patients acceptable to their general practitioners and the prescribing advisers I think it would be advisable that these patients are treated within the context of a clinical study. This would have the benefit of being able to demonstrate informed consent and would reassure your fellow practitioners and commissioners that there was a scientific basis and measurable outcomes to your work. In addition this would make available the context of framework within which these patients are treated.

We welcome your views on this.

Yours sincerely,

Dr Michael Kelsey
Consultant Microbiologist & Chair of the Drug & Therapeutics Committee

Dr Bridget Coleman
Deputy Chief Pharmacist

cc. Dr Helen Taylor, Head of Pharmacy
Martin Machray, Director of Quality and Integrated Governance
Amalin Dutt, Head of Medicine Management
Dr Gillian Greenhough, Chair, Islington CCG

UCL DIVISION OF MEDICINE
WHITTINGTON HOSPITAL CAMPUS
Research Department of Clinical Physiology

28 October 2015

Dr Michael Kelsey
Whittington Health NHS Trust

Dear Michael

Thank you very much for your letter and for the discussion that we had about this matter.

I am being referred patients who are suffering from chronic recalcitrant urinary tract infections which have affected them for an average of five to six years. They have not responded to treatments advocated in the various guidelines. These people occupy the long tail of a positively skewed distribution where the guidelines only address the first two quartiles of the distribution.

I should be failing as a doctor if I were to deny such patients treatment because their needs were not covered by guidelines. I am obliged to manage these people, to the best of my ability, using all of the advice and knowledge that is available to me. I believe that I am doing so. I am very well aware of the risks associated with my strategies as are my patients. They are therefore supported by very easy rapid access to my advice

Be that as it may, I am going to put my practice, before the ethical committee for their consideration. I am sure that they will be pleased to provide their advice on the matter. This would be much more efficient than attempting a CTIMP approval, which as I explain below, would be inappropriate. In the meantime, I shall continue to treat these patients, as I have described to you, on the fact of their deterioration when the current regimes are tempered or discontinued. You are aware that I have made many efforts to simplify and terminate treatment but with frequent adverse outcome for the patients. I attach the protocol that my unit uses and which I sent to you earlier.

I am concerned, I am wholly willing to provide the necessary prescriptions for the patients. I should not expect a GP to take over this responsibility. I own that patients coming from afar will seek such cooperation from their GPs.

I should also advise that my approach to practice is not speculative. Our basic scientific discoveries and my clinical practice has been described in the published literature. The latter in the proceedings of the International Continence Society (2010 to 2012) and comprehensive paper is being sent to referees this summer. I attach a paper that I sent to Helen Taylor, Bridget Coleman, yourself and others earlier this year, which covers these data.

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UCL DIVISION OF MEDICINE
WHITTINGTON HOSPITAL CAMPUS
Research Department of Clinical Physiology

We have two RCT trials of our first-line approach to chronic urinary tract infection, extant at this time. These are placebo controlled trials of Nitrofurantoin. Nevertheless it took us four years to get these Clinical Trials of an Investigational Product (CTIMP) through the NHS R&D bureaucracy. The contemporary costs and time investment for a CTIMP are huge so that US Preventive Services Task Force (USPSTF) Level I evidence will inevitably take several years to accrue. In such circumstances I am proud to be working from USPSTF Level II-2 evidence. If the summer paper is published we shall have reached NHS level A.

With best wishes

James

James Malone-Lee MD FRCP
Professor of Medicine

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Draft Minutes of Chronic LUTS prescribing meeting

Wednesday 22 January 2014, 4-5pm.

Seminar Room, Pathology Level 5, Whittington Hospital

Attending:

Mr Amalin Dutt (AD), Head of Medicines Management, Islington CCG (Chair)

Dr Chris Cooper (CC), Medicines Optimisation Lead GP, Islington CCG

Dr Michael Kelsey (MK), Consultant Microbiologist, Chair of Whittington Drugs & Therapeutics Committee

Ms Ai-Nee Lim (ANL), Antimicrobial Pharmacist, Whittington Health

Ms Fiona Isaacson (FI), Director of Operations, Surgery Division (representing Mr Nick Harper, Divisional Director of Surgery)

1. Introductions and background

   AD introduced the meeting and explained that the meeting had been convened following a series of concerns raised by GPs regarding requests for long-term and varied antibiotic prescriptions for patients seen by Professor James Malone-Lee at the Whittington Hospital.

   The purpose of the meeting was to seek assurance from Whittington Health as to their arrangements for antimicrobial stewardship and review of this prescribing and to ensure patient safety.

   MK declared a competing interest in that he has co-authored a number of papers regarding Chronic LUTS with Professor Malone-Lee. No further competing interests were declared.

   AD highlighted that GPs were primarily concerned about the evidence base for use of these regimens, the potential risk of *C.difficile* infection arising from such prescribing and whether this form of prescribing would better be undertaken as part of a research project or clinical trial. GPs had asked that

they should not be asked to take on this prescribing without assurance of an appropriate governance framework.

AD provided a summary of the correspondence to date between Islington CCG and Whittington Drugs & Therapeutics Committee (Appendix 1). Following the last letter from the CCG to the Trust, the matter had been escalated to Mr Martin Kuper, Medical Director and Mr Nick Harper, Divisional Director of Surgery. Following discussion with Mr Harper, it had been agreed that an initial meeting to review the concerns raised would be helpful with a view to meeting with Prof Malone Lee for further discussion. FI was attending representing Mr Harper.

2. Current arrangements for Chronic LUTS prescribing and prescribing governance at Whittington Health

   AD asked MK, FI and CC to provide their perspectives regarding current arrangements for Chronic LUTs prescribing and prescribing governance at Whittington Health.

   MK emphasised that the patient cohort under review by Professor Malone-Lee has failed all other treatments and is suffering from chronic lower urinary tract symptoms (LUTS). Many of the patients seen by Professor Malone-Lee report some success with treatment although there is no trial data or audit data available. MK highlighted that this is a common condition, presenting in 7% of consultations. The criteria for definition of a urinary tract infection date back to the 1950's and 1960's. Bacteriuria can be confirmed if a single bacterial species is isolated in a concentration greater than 100,000 colony forming units per millilitre of urine. Many of the cohort do not demonstrate bacteriuria under these criteria but continue to complain of symptoms. Professor Malone-Lee's hypothesis is that the infection may be intracellular and reside within the lower levels of the layered epithelia. There is not as yet robust evidence to support this hypothesis. MK noted that a large proportion of organisms detected are enterococci.

   MK has written to Professor Malone-Lee to highlight the research nature of the treatment protocols and to encourage development of an appropriate clinical study. Professor Malone-Lee has responded highlighting the difficulties in conducting and obtaining funding for a research study. MK noted that Professor Malone-Lee is employed by UCL.

   FI commented that there is also a need to be clear when a treatment course is completed. FI also noted that patients may be admitted to hospital if their symptoms are not controlled adequately.

   AD asked what safety information was available regarding these regimes.

MK was aware of one case of *C.difficile* in a patient being treated by the service and one death (causality not known). There may also be a case of interstitial lung disease associated with nitrofurantoin prescribing.

MK highlighted that the Drugs and Therapeutics Committee may not be the most appropriate Committee for discussion of these issues and therefore the matter had been escalated to Medical Director level. A referral to the GMC may be needed to assess from a professional perspective appropriateness of an individual doctor's treatment approach where this was not in line with conventional practice.

FI highlighted the concerns from the Surgical directorate and that initial discussions had taken place between Mr Harper and Professor Malone-Lee.

ANL commented from a pharmacy perspective that the long term antibiotic prescriptions were unusual and they would normally challenge prescriptions over 14 days duration. Doses of nitrofurantoin were also outside of the Summary of Product Characteristics recommendations.

CC commented that communication from Professor Malone-Lee is excellent. Letters are thorough and complete; there is a clear management plan and arrangements for review and follow-up. GPs were not comfortable however with taking on the prescribing recommendations as they were outside current recommended practice and guidelines.

AD emphasised that CCG guidelines make it clear that there may be patient exceptions and these may be reported to the CCG as a practice audit. The concerns with the LUTS prescribing were related to safety and appropriateness and not to achievement of targets.

MK commented that the data missing is the incidence of *C.difficile* and any problems arising from the use of nitrofurantoin. AD commented that this could be collected by retrospective case-note audit.

3. Future arrangements and options for clinical governance and antimicrobial stewardship

   MK commented that the LUTS antibiotic prescribing would likely need to be taken forward as part of a clinical study. MK suggested that a peer group review could make the recommendation for a hospital funded study.

   AD emphasised that there should be no more requests for GP prescribing and that an audit of patients would help assure safety of current practice.

FI commented that it would be challenging to stop all patients treatment although this would take place if deemed unsafe.

CC commented that (although the patients attending the clinic were mostly female and mostly being treated with antibiotics) there were also a small number of male patients and also of patients on long term antifungal treatment.

4. Summary and next steps

AD thanked the group for their comments and participation.

Actions:

1. FI to inform the responsible person for Whittington Health.
2. The group agreed that there is concern over a number of issues:
    a. Evidence-base
    b. What is the patient pathway?
    c. What is the incidence of complications?
3. Professor Malone-Lee to be asked to present to a panel on this service and research, including any information collected regarding outcomes and complications.
4. The key questions to be addressed with respect to the science behind the treatment protocols are:
    a. Why do you think this science applies to this group of patients?
    b. What is the rationale of this treatment?
    c. What do you think you would need to do to convince the medical body that this is a valid approach for this group of patients?
5. FI to explore convening an appropriate panel, AD to approach Professor Liam Smeeth, Chair of the Islington Medicines Optimisation Group, to join the panel as he has extensive experience of primary care research and epidemiology.

Print Close

Fwd: 15228 Islington CCG - FOI request

From: **Rosie Sarrington** (rosiesarrington@btinternet.com)
Sent: 07 November 2015 10:01:50
To: Holly Boyd (holly.s.boyd@hotmail.com)

10 attachments
The treatment of chronic urinary tract infection in Professor Malone-Lee.pdf (64.6 KB) , Protocol for management of patients with chronic lower urinary tract symptoms with clinical evidence of urinary tract infection.pdf (30.3 KB) , Minutes of chronic luts meeting Wednesday 22 January 2014.pdf (173.4 KB) , malone-lee4.pdf (75.6 KB) , Letter to Michael Kelsey 28 Oct 2015.pdf (76.4 KB) , jml clinic letters.pdf (281.3 KB) , 131003 - ML response.pdf (221.2 KB) , 130503 - antibiotic prescribing for chronic.pdf (109.0 KB) , Ref 15228 FOI Corraspondance.pdf (702.0 KB) , Ref 15228 Response.pdf (169.7 KB) ,

Sent from my iPhone

Begin forwarded message:

From: Jill Brice <jillbrice@hotmail.com>
Date: 30 October 2015 10:15:22 GMT
To: "rosiesarrington@btinternet.com" <rosiesarrington@btinternet.com>
Subject: FW: 15228 Islington CCG - FOI request

Rosie, I asked them to convert to Word as also couldn't read them. This is what they have sent me. However as you can see the original contained 26 files and this is only 10, so I hope that they've just joined a few together for ease. I am still trying to read the original somehow to make sure that they are all included.

The following is being advised to Prof patients by someone posting on COB. Were FB patients to do the same would it in any way interfere with legal action?

"So whilst the MPs, Councillors and Scrutiny Committees will most definitely help gather momentum over this issue (and may well eventually resolve the issue by insisting the Whittington support the Professor and permanently re-open the Clinic), too much damage may already have been done for too many patients by then... So PLEASE also register a formal complaint on-line with the GMC this week as this should illicit a response within 7 days - and even if they would otherwise be reluctant to investigate a doctor's indirect actions which have only 'indirectly' affected a patient, if they get a deluge of complaints all about the same doctor I think they would be left with no choice but to urgently investigate."

Jill

From: ISLCCG.FOIISLINGTONCCG@nhs.net
To: jillbrice@hotmail.com
Date: Thu, 29 Oct 2015 13:55:52 +0000
Subject: RE: 15228 Islington CCG - FOI request

Hi Jill,

Apologies that I wasn't able to get this information to you yesterday
Please see all the information you requested attached

Kind Regards,

Shivani Patel
Communications and Member Relations Officer

Islington Clinical Commissioning Group

338-346 Goswell Road

London

EC1V 7LQ

0203 688 2973

From: Patel Shivani (NHS ISLINGTON CCG)
Sent: 28 October 2015 14:28
To: Jill Brice
Subject: RE: 15228 Islington CCG - FOI request

Hi Jill,

Thank you for your email

As discussed on our telephone conversation, I would have to see what the problem in opening up your response was and if there was anything on the shared drive I would send it to you with a matter of urgency.

No, I am not wrong when I said the FOI process would have to start again if the information was not immediately accessible and no, Mr Wuestefeld-Gray should not have to respond back to you in order to ask how you would like your information to be presented.

The Freedom of Information Act 2000 states that all raw material should be sent to the requester un the original format unless the requestor has specified otherwise.
In this care the raw data has been sent in the format of emails.

As I appreciate you may be against tight deadlines , I have offered you a good will gesture in prioritising your request over my other work - so please give me a little time to figure of what the problem is.

I have on the shared drive all of the information that Mr Wuestefeld-Gray has sent to you. It seems the reason he has sent it to you in a folder is because there are approx. 20 emails that would have been difficult to send to you individually.

To resolve this, I will either find what the barrier is that is preventing you to view the information or I will copy these emails and send it to you in a PDF format for your ease

I will have this to you by end of play today.

Please confirm you have received this.

Kind Regards,

Shivani Patel
Communications and Member Relations Officer

Islington Clinical Commissioning Group

338-346 Goswell Road

London

EC1V 7LQ

0203 688 2973

From: Jill Brice [mailto:jillbrice@hotmail.com]
Sent: 28 October 2015 14:04
To: Patel Shivani (NHS ISLINGTON CCG)
Subject: 15228 Islington CCG - FOI request

Dear Shivani Patel,

15228 Islington CCG - FOI request

I have just spoken to the ICO.

A) you are quite wrong when you say that the whole process of FOI request will have to start again. The ICO told me that the documents should be converted without delay.

B) At the time I made the original request, Mr Wuestefeld-Gray should have asked us in

what format I would like to receive the information.

Please expedite this. For your convenience I attach the file.

Please also acknowledge receipt of this message.

With kind regards,

Jill Brice

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