We treat patients who present with chronic bladder pain, chronic pelvic pain, recurrent urinary infection, voiding problems and overactive bladder symptoms. These complaints overlap considerably and usually there is shared aetiology.

Our typical patients describe a similar story, lasting an average of 6.5 years that commenced with an acute UTI this responded partially to a short antibiotic course (3 days to 14 days). Most have been exposed to repeated courses, but these have ceased in the face of normal urinalyses, despite persisting symptoms. They have continued to suffer low-grade lower urinary tract symptoms including bladder pain, with symptoms fluctuating and acute exacerbations several times a year. Urinalysis has usually been negative and the investigations; including urodynamics, cystoscopy, bladder biopsy, renal tract ultrasound, CT and MRI scans, have been unhelpful apart from the biopsies manifesting inflammation of the bladder mucosa. The patients have been diagnosed with interstitial cystitis or chronic bladder pain syndrome. They have failed to respond to cystodistension, urethral dilation, antimuscarinics, bladder instillations, Elmiron and various short-course and prophylactic low-dose antibiotic regimes. It is quite common for their symptoms to be attributed to psychological origins.

The most probable current explanation is that patients experience an infection of the bladder that involves parasitisation of the lining, urothelial cells going deep into the base of the urothelium. The affected cells signal their distress and an inflammatory reaction starts. The inflammation irritates the bladder causing frequency and urgency. Pain will also feature and the longer that the inflammation persists the more complex that experience. 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 chronic disease. A recurring feature of the history is that the patients, convinced of a urine infection, are confounded when their urine tests negative. The routine tests used to check for urine infection in most health services 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. First-line, we use a microscope to examine immediately fresh urine and count the white blood cells and the urothelial cells being excreted in the urine.

The microscope findings are far from perfect and during treatment, the urine will clear, although infection persists. From that time we rely on symptoms. It is not always necessary to check the urine to assess progress. It is the patients’ symptoms that are all important, no tests are superior. We are also dependent on the patients’ descriptions of their responses to treatment and the effects of different doses. The direction of change of symptoms is a very important guide.

The evidence we have, traces the problem to deep-seated infection by 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 chronic 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 in the permitted ranges. Low-dose, once daily regimes are not reliable. Chronic ingrained infections require long treatment courses. We shall check that a treatment is appropriate by first seeing an improvement. We then stop treatment briefly and check for signs of relapse. That way we validate the antibiotic prescription for the individual patient. The infections are commonly mixed and one antibiotic may be insufficient. Nowadays we overcome this problem most of the time by using the disinfectant Methenamine (Hiprex). However, a second antibiotic may be necessary but it will be used only if it is endorsed by improved response which reverses when this is withheld. You will find that we will question you closely about the effects of a prescription on your symptoms and the occurrence of side effects. 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.

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. 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, preferably spread over the day, 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 a dormant infection where the microbes are not dividing is not susceptible to antibiotic treatment and their annihilation depends on shedding of the infected cells into the urine.

We have much data from longitudinal treatment studies. These show that the cell-associated infection of the bladder wall subside gradually. This is associated with slow clearance of the urinary white blood cells, but the symptoms’ clearance lags 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 science. The symptoms are not caused by psychological problems and they are not imagined. Hypnosis and psychoanalysis have failed those who have been treated by them.

The value of urethral dilation or bladder dilation is without evidence 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 in both genders. 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 less sensitive bugs grow to occupy the vacated space. Usually these opportunistic colonies are harmless bugs that
usually live in the person. If however a pathogen spreads, symptoms will develop but these may be different because the species is not the same. If there is solid evidence that the current antibiotic is effective we do our best to maintain it, first of all by increasing the dose as the first option for dealing with insensitivity. We may decide to layer in a second agent if that is indicated. 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 cell counts 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 average length of treatment with antibiotics is about one year. 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 the infection being treated. From time to time acute exacerbations or flares may occur because the bladder may struggle to cope for a short period. These flares 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. We have to prescribe outside of guidelines because our patients have failed to respond to treatments that follow guidelines. 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 data 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. All treatments carry risks and protracted courses of treatment pose
particular concerns. We must decide on the treatment courses by drawing on our patients’ views and understanding of the risk-benefit ratio. We shall therefore talk about the risks and provide information on adverse risks associated with all our prescriptions. We maintain very close safety monitoring and provide a rapid response service for patients to report side effects or concerns about toxicity. Nowadays, there are particular concerns about the misuse of antibiotics and the rise of resistance. We are all too aware of this and must work with great care but our patients need these treatments if they are to recover. In fact, we see remarkably little antibiotic resistance. We monitor isolates all the time for the evolution of resistance and the data are most reassuring. It is not possible for patients to become resistant to a treatment.

An important concern is C.Diff diarrhoea. A while ago we 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, most being first generation, narrow spectrum agents. 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.

There is evidence that probiotics can help with antibiotic effects on the bowel.

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. Today much salient diagnostic, pathophysiological and clinical treatment data are in peer-reviewed journals. There are more data on the way which continue to support our methods.

In treating our patients, we are not experimenting on them without their knowledge. We advise treatment based upon the best available evidence, drawing on the published literature and the data generated through our clinical and basic science research. We do not waste any of the data that we obtain from our patients during treatment. These are anonymised and fed into statistical analysis systems allowing us to spot clusters and patterns in symptoms, treatments and their responses. By those means we learn from successes and failures whilst administering our normal care. This process has played a very large part in the development of our approach to treatment. Some patients may be asked to consider participating in some clinical research but there will never be any obligation and refusal to participate would not influence further treatment in this centre.
What should our patients expect?

Your treatment will be based on your symptoms, your recall of the influence of individual antibiotics, whether good or bad, and urinalysis by microscopy of a fresh specimen of urine examined immediately using a light microscope. We shall count the urinary white cells (pus cells) and the urinary epithelial cells. Many patients have been advised wrongly, to drink plenty of fluids and so their urine is dilute at first attendance, because of this the urinalysis is negative but not to worry, the symptoms analysis that we use is extremely accurate.

You are very likely to be prescribed an antibiotic and you will learn that we shall do our utmost to select the older, first generation, narrow spectrum antibiotics. It is also probable that we shall try to combine the antibiotic with the urinary disinfectant Methenamine (Hiprex) which has the effect of turning your urine into a germ killer just like Detol. Understand that urine cultures are unreliable and do not provide adequate data on the microbial infection and its sensitivities. Thus we shall base treatment using assessments of the probability of efficacy based on previous history, symptoms, signs, urinalysis and historical data collected from treating similarly affected patients. Your anonymised data will be used to feed that record of accumulated experience. We shall judge the efficacy of the prescribed treatment by plotting graphs of your symptoms score and the results of urinalysis by microscope. You will find that we shall question you closely about the variation of your symptoms in relation to the dose of the antibiotic used and alter the dose accordingly. We shall ask about side effects a great deal. We shall alter your treatment if we do not see efficacy or if side effects are a problem. There will be a certain amount of trial and error elimination in working out the right treatment for you. Even when you have been established on an apparently effective regime we shall test the justification for using it by stopping it to see if the symptoms come back. We shall discover the correct point from when you shall not need further antibiotics by stopping treatment and seeing how you get on. Once again, this will be a process of trial and error because the biological signals in the urine recover sometime before the symptoms and before the need for antibiotic treatment has ceased.

The antibiotic and Methenamine combination is going to be prescribed for a long time because we have found that it takes an average of a year to clear the chronic ingrained urinary infections seen here. Thus in the early days we shall focus on finding a regime that you can tolerate and which is effective on your symptoms. We shall be concerned about side effects because they make protracted treatment intolerable despite them being acceptable in a short-term course.

To illustrate the sort of story that you might expect we show below a plot of the urinalysis data taken from a patient (Figure 1). We also show the plot of the symptoms scores.
It plots against time the urinary pyuria (white blood cells or pus cells) and the symptoms. The patient aged, 42, had suffered undiagnosed chronic urinary infection for two years. She was treated by us with antibiotics over three years (2013 to 2015). 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 (Figure 2). 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 six visits.

Antibiotic treatment for these periods of time presents more risks than those associated with short courses given for acute symptoms and we must stay alert to that. We work hard at safety and have evolved the least toxic regimes that we can achieve whilst still securing efficacy. That is why we tend to stick to the older, first generation, narrower spectrum antibiotics. If a patient has an illness that requires an antibiotic to treat them then the prescription should be appropriate for the period that is necessary. We have to test that by stopping the medication and restarting if the symptoms recur. We shall ask you about side effects whenever you are reviewed and out email service is there for you to report adverse events and efficacy failures. The lutscommunityadmin.whitthealth@nhs.net email address is monitored all of the time and we usually get back to you within 24-hours, however we plead with all of you to use it with care, it can very easily become overwhelmed by demand. Side effects and toxicity can be safely managed through careful communication between doctor and patient.
Figure 1 – The symptoms and urinalysis for white blood cells recorded each visit for one patient.
Figure 2 The frequency distribution of the number of visits to the service required by our patients