

# Antibacterial agents and urinary tract infection: a paradox

**D**ESPITE the dramatic improvements in the treatment of urinary tract infection achieved with antibacterial agents, the condition remains. It is believed to be the commonest bacterial infection,<sup>1</sup> it is still an important cause of renal failure, and the symptoms associated with it remain troublesome to patients of both sexes and all ages. Why is this so, and is there any evidence that antibacterial agents themselves play an adverse role in the natural course of the condition?

Urinary tract infections are usually caused by organisms present in the commensal flora of adjacent sites, most commonly the bowel. In their natural sites these organisms exist in equilibrium with others, fulfilling a beneficial function. The defensive properties of the commensal flora of the distal urethra against invasion by bowel organisms almost certainly include production of inhibitors against potential pathogens, coaggregation of commensal species with each other or with potential pathogens,<sup>2</sup> colonization of epithelial surfaces and competition with potential pathogens for sites of adhesion.<sup>3</sup> The trigger for successful invasion of the urinary tract may be local trauma, such as occurs during sexual intercourse, failure of the washout mechanism (an important natural mechanical defence), or direct introduction of organisms by catheters or instruments.

The desired effect of antibacterial treatment — eradication of pathogenic bacteria from the urinary tract — is likely to be accompanied by an effect on the commensal flora throughout the body. The nature of this effect depends upon the antibacterial spectrum and pharmacokinetic properties of the agent used and the duration of treatment. Important factors in the balance between benefit and harm are the composition of commensal flora, the site of infection (whether in the urine only or involving tissue) and the presence of any predisposing mechanical factor such as an indwelling catheter.

There is growing evidence that antibiotics can adversely affect the natural course of urinary tract infections in patients. There are important general differences between the different classes of antibiotics used. Broad spectrum penicillins select resistant Gram negative organisms in the bowel flora and destroy the commensal flora of the distal urethra<sup>4</sup> (including lactobacilli which first appear in women at this site at puberty), thus facilitating colonization of the urethra and possible bladder infection with resistant Gram negative organisms. Narrow spectrum penicillins, although not selecting resistant bowel organisms, may predispose to Gram negative infection by destroying the urethral commensal flora. This could account for the strong clinical impression, not known to be documented, that children tend to get urinary tract infections soon after upper respiratory tract infections which are often treated with penicillins.

Sulphonamides and agents containing trimethoprim do not usually select resistant bowel organisms except in some places where resistance is high. They leave the urethral flora of children unchanged,<sup>4</sup> thus protecting against Gram negative colonization. In adult women, however, they upset the balance of the urethral flora, often allowing lactobacilli to multiply disproportionately.<sup>5</sup> These organisms may then extend to the proximal urethra and into the paraurethral glandular tissues.<sup>6</sup> Many patients treated with these agents develop the symptoms of urethral syndrome — dysuria, urgency, urge incontinence, a feeling of perineal pressure and sometimes dyspareunia — a more upsetting and intractable clinical condition than the cystitis for which

they were originally treated. Similar bacteriological changes occur in adult women treated with the new fluoroquinolones,<sup>7</sup> to which lactobacilli are also resistant. As yet, there are no published data on the possible clinical consequences. Nitrofurantoin has the advantage that it is rapidly absorbed from the bowel and excreted only in the urine, with little or no effect on the bowel flora. The effect of nitrofurantoin or of the cephalosporins on the urethral flora has not been documented, but some patients treated with these agents, especially those on long-term low dose prophylaxis, develop urethral syndrome (unpublished results).

In some patients bacteriuria is inevitable, for example those with an indwelling catheter for more than a few days (when organisms have direct access to the bladder) or those with neuropathic bladders or ileal conduits (in whom there is no effective washout mechanism). It is probably also reasonable to include elderly women who have suffered from a lifetime of cystitis in this group. In patients with longstanding infection organisms may become embedded in the bladder wall,<sup>8</sup> making them inaccessible to effective concentrations of antibiotics. Administration of antibiotics to patients with inevitable bacteriuria will not render the urine sterile for longer than a few days.<sup>9</sup> The bacteriological consequences will depend upon the type of agent used. Resistant bowel organisms, for example pseudomonas or klebsiella, and resistant urethral commensals such as corynebacteria<sup>10</sup> may be selected, and the clinical consequences include ascending renal infection<sup>11</sup> and infection and inflammation of the prostate in men and of the paraurethral tissues in women.

What practical relevance have these facts to the use of antibacterial agents for the treatment of urinary tract infections? In general, courses of antibiotics should be short — three days is sufficient for treatment of acute cystitis in women — and the value of an agent such as nitrofurantoin which has little or no effect on the bowel flora should be considered. When longer treatment is required, for example for tissue infections such as pyelonephritis or prostatitis, the effect of such treatment on the commensal flora should be remembered as a possible cause for any symptoms persisting after treatment. Patients should not be treated with antibiotics repeatedly without bacteriological confirmation of infection with bladder pathogens. Many of those with persistent symptoms have urethral syndrome. If antibiotics are given repeatedly and in prolonged courses the upset in the urethral flora may result in long-term damage to the tissues, including, in advanced cases, the intractable condition of interstitial cystitis.<sup>12</sup> Antibiotics should not be given to patients with inevitable bacteriuria at times when they are well. The episodes of clinical infection to which they are prone can then be treated promptly and effectively because the infecting organisms will be sensitive to a variety of antibacterial agents.

If microbiology laboratories undertake culture techniques which detect commensals such as lactobacilli as well as the aerobic bowel organisms an explanation may be found in most patients presenting with symptoms suggesting urinary tract infection. A rational explanation may then be given to the patient for withholding antibiotics when lactobacilli are isolated. Specimens from patients with inevitable bacteriuria should only be taken when treatment is required, for example when the patient is feverish, and the general practitioner should make this

clear on the request form. Knowing that treatment is indicated, the laboratory should provide information on antibacterial sensitivities as soon as possible.

Good communication between microbiology laboratory staff and general practitioners is essential if the correct balance between advantage and disadvantage of the use of antibacterial agents in the treatment of urinary tract infection is to be achieved.

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# Do therapeutic interventions stand the test of time?

**M**ANY therapeutic interventions demonstrate a pendulum of usage. After 30 years, anticoagulant drugs are again popular for a variety of indications while the use of lignocaine, still controversial in treating acute myocardial infarction, appears to be on the wane. The vicissitudes of digitalis are evident in the pages of medical journals, the pros and cons punctuated by an occasional outburst of enthusiasm about its use for congestive cardiac failure.<sup>1</sup> Finally, in the hands of plastic surgeons, the leech is enjoying a modest comeback.<sup>2</sup>

An upswing in usage is easy to understand and may be the result of fresh information or a serendipitous discovery extending the scope of a drug or procedure. Beta blockers were employed for nearly a decade for angina and for supraventricular arrhythmias before they came into widespread use as a first line therapy for lowering blood pressure. More recent indications include migraine headache, thyroid disease and portal hypertension. Coronary bypass surgery was originally performed for intractable ischaemic pain that interfered to an intolerable extent with the patient's lifestyle. Today, it is often used for averting sudden death in people with extensive coronary heart disease who are only mildly symptomatic.

The downswing of the therapeutic pendulum is harder to comprehend. What is the reason for the apparent waning of efficacy over time, a phenomenon that might be called herd tachyphylaxis? First, there is the loss of placebo influence, a process of familiarity breeding contempt. This is reinforced by state-of-the-art knowledge imparted to doctors by visiting representatives for drug manufacturers who are always abreast of the failings of other companies' products. Thus, the enthusiasm with which the preparation is dispensed may lessen, and with it the power of suggestion.

Secondly, there is the process that could be referred to as dilution of indications which is the reverse of expansion of scope. Many people are now experiencing chest pain within a few years of having coronary bypass surgery.<sup>3</sup> As a result, the operation

appears less successful than was originally hoped. However, our protocol for investigating patients who have sustained a myocardial infarction has grown ever more aggressive and some patients are referred to a surgeon when asymptomatic or with only mild symptoms. Thus, prevention of a further infarct has become the outcome measure rather than relief of chest pain, the recurrence of which may wrongly suggest failure. The same applies to propranolol, as its uses proliferate and the diagnoses for which it is prescribed become further removed from its best known pharmacological activity. Propranolol is prescribed for both angina pectoris and stage fright; if the drug is ultimately shown to be less effective for the latter than initially thought, its reputation regarding the former may be tarnished too.

Thirdly, there is the question of what we are treating and the extent to which the diagnosis has been refined. Nitrates are prescribed when the patient gives a history consistent with angina pectoris. A stress test or angiogram are not carried out since these can only support or diminish the likelihood that angina is present; the report of symptoms is the decisive factor.<sup>4</sup> In effect, the response to a nitrate may be looked upon as furthering the diagnosis. Similarly, if a patient presents with symptoms suggesting a peptic ulcer, a therapeutic trial is regarded as a cost effective approach, with gastroscopy reserved for those for whom drug treatment is ineffective.<sup>5</sup> In both cases, there is no gold standard for the diagnosis. A normal angiogram does not exclude spasm as a possible cause of angina and the correlation between gastroscopic findings and report of pain in patients with a peptic ulcer is known to be poor.<sup>6</sup> Thus, a precise diagnosis is virtually impossible and there always exists the possibility that a patient with chest pain who responds to nitrates or one whose dyspepsia is alleviated by H<sub>2</sub>-receptor blockers may have another condition which these drugs may improve.

Urinary tract infection is a self-limiting disorder, and thus treatment with antibiotics must be considered palliative. A respected textbook of primary care states that antibiotics may