cystitis in patients with creatinine clearance > 60 mL/min (avoid in women who are 36+ weeks pregnant). In patients with renal impairment or known intolerance or allergy to nitrofurantoin, use trimethoprim 300 mg, once daily for three days in females (avoid during the first trimester of pregnancy) and seven days in males. If there is a known high rate of resistance to trimethoprim in the local area, consider taking a urine sample; future treatment can be guided by this.

While norfloxacin is an alternative antibiotic for the treatment of cystitis, it should be strictly reserved for isolates resistant to trimethoprim or nitrofurantoin.[7] Norfloxacin should be avoided in pregnant women or in patients who have severe renal impairment (refer to the New Zealand Formulary for details).[6]

For further information about the use of norfloxacin see: "Quinolone antibiotics – limit use", BPJ 35 (Apr, 2011).

References

1. Medicines and Healthcare product Regulatory Agency (MHRA). Nitrofurantoin now contraindicated in most patients with an estimated glomerular filtration rate (eGFR) of less than 45 ml/min/1.73m^2. MHRA, 2014. Available from: www.gov.uk/drug-safety-update (Accessed Oct, 2015).
2. New Zealand Medicines and Medical Devices Safety Authority (Medsafe). Minutes of the 163rd medicines adverse reactions committee meeting – 10 September 2015. Medsafe, 2015. Available from: www.medsafe.govt.nz (Accessed Oct, 2015).
3. W. M. Bamford & Company Limited. Nifuran. Medicine Datasheet, 2004. Available from: www.medsafe.govt.nz (Accessed Oct, 2015).
4. Scottish Intercollegiate Guidelines Network (SIGN). Management of suspected bacterial urinary infection in adults. Edinburgh: SIGN, 2012. Available from: www.sign.ac.uk (Accessed Oct, 2015).
5. Auckland District Health Board (ADHB). Adult empirical antimicrobial treatment guidelines. ADHB, 2014. Available from: www.adhb.govt.nz (Accessed Oct, 2015).
6. New Zealand Formulary (NZF). NZF v40. 2015. Available from: www.nzf.org.nz (Accessed Oct, 2015).
7. bpacnz. Antibiotics: choices for common infections. Available from: www.bpac.org.nz (Accessed Oct, 2015).
8. Kanji Z, Su VCH, Mainra R. Nitrofurantoin-induced pulmonary reaction involving respiratory symptoms: case report. Can J Hosp Pharm 2011;64:362–5.
9. The Institute of Environemental Science and Research Ltd (ESR). Antimicrobial resistance data from hospital and community laboratories. ESR, 2013. Available from: https://surv.esr.cri.nz/PDF_surveillance/Antimicrobial/AR/National_AR_2013.pdf (Accessed Oct, 2015).

CORRESPONDENCE

Should antibiotics be continued for a sore throat if GAS negative?

Dear Editor,

There are occasional exceptions to every rule, including Mark Thomas' generally good advice to stop antibiotics if a throat culture fails to confirm GAS. Throat cultures, if properly taken, are 90-95% sensitive for GAS, not 100%, and that is only if they are properly taken from the tonsils and the posterior pharynx. If a child has a classic appearance with fever, tachycardia, dusky red moist tonsils, tonsillar pillars and pharynx, quite large neck nodes, a bit of a scarlatiniform rash, and the complete absence of nasal or chest symptoms, I would want that child to complete ten days of antibiotics regardless of the swab result.

Dr Ronald Baker [Online comment]

Dear Editor,

Mark Thomas might spare a thought for the mountains of unused antibiotics that might appear in vulnerable households from those who stop a ten day course early. Surely this is a greater risk than one unnecessary but properly completed course. While awaiting swab results a more practical option might be to prescribe a five day course with one repeat available at no extra charge if the swab returns positive.

Is near-patient testing for GAS likely to become a practical option in New Zealand? And how did the UK manage to eliminate rheumatic fever from its morbidity profile?

***Dr David Smith,** General Practitioner*
Pahiatua
(Personal view only)

Response from Associate Professor Mark Thomas:

I recently strongly advised that antibiotic treatment should be promptly discontinued in a person at high risk of rheumatic fever, with a sore throat, who has a negative swab for *Streptococcus pyogenes* ["*Should antibiotics be continued for a sore throat if GAS negative?", Correspondence, BPJ 69 (Aug, 2015)*].

Dr Baker suggests that because culture of a throat swab is *only* 90–95% sensitive, he would advise patients with many clinical features associated with streptococcal pharyngitis to complete a ten day course of treatment. However, such clinical findings are not more reliable than culture as evidence that pharyngitis is due to *S. pyogenes*. Clinical prediction rules can help to indicate which children with a sore throat are most likely to have *S. pyogenes* isolated from a throat swab. However, none of these clinical prediction rules is either very sensitive or very specific. A recent study of the most effective clinical prediction rule[1] in children in Brazil, found that *S. pyogenes* was present in only 41% of children with the highest test scores.[2] Use of this and other clinical prediction rules is not much better than a coin toss, and certainly very much less reliable than laboratory culture results!

Dr Smith suggests that "mountains of unused antibiotics" might accumulate in the households of people at high risk of rheumatic fever, and these unused antibiotics might pose a greater risk to the family members than consuming five or ten days of an antibiotic course, prescribed for an infection that is not present. A simple solution to this problem is to advise patients not to have the antibiotic prescription dispensed unless informed by the practice that the throat swab is positive. To suggest that a patient who does not have *S. pyogenes* infection should be the disposal unit for an unnecessary course of antibiotics seems surprising to me. While putting the unneeded antibiotics in the rubbish or down the lavatory will make a small contribution to contamination of a landfill or of the waterways, surely that is better than advising the patient to consume the antibiotic when there is no expectation of any benefit for the patient and only the risk of an adverse event, such as diarrhoea or rash, and disruption of their normal microbiome?[3, 4]

Dr Smith also asks whether near patient testing, using a rapid antigen detection test is likely to become a practical option in New Zealand. A recent study of one such test found that of 61 school children with *S. pyogenes* cultured from a throat swab only 22 had a positive rapid test (sensitivity 36%), and of 237 school children who did not have *S. pyogenes* cultured from a throat swab 37 had a false positive rapid test (specificity 84%). This particular test was considered insufficiently robust for routine use in school based clinics.[5]

Associate Professor Mark Thomas
Department of Molecular Medicine and Pathology
Faculty of Medical and Health Sciences
University of Auckland

References:

1. Le Marechal F, et al. Streptococcal pharyngitis in children: a meta-analysis of clinical decision rules and their clinical variables. BMJ Open 2013;3:e001482.
2. Joachim L, et al. Pragmatic scoring system for pharyngitis in low-resource settings. Pediatrics 2010;126:e608-e614.
3. Saari A, et al. Antibiotic exposure in infancy and risk of being overweight in the first 24 months of life. Pediatrics 2015;135:617-26.
4. Gough EK, et al. The impact of antibiotics on growth in low and middle income countries: systematic review and meta-analysis of randomised controlled trials. BMJ 2014;348:g2267:1-13.
5. Upton A, et al. Disappointing performance of rapid antigen detection tests for group A streptococcus in the Auckland school-based sore throat programme. N Z Med J 2014;127:1389; 103-5.

Comment from bpac^{nz} editorial team:

In his letter, Dr Smith was also making reference to another article which appeared in the same edition of BPJ – "Piles of pills: prescribing appropriate quantities of medicines", BPJ 69 (Aug, 2015). If a medicine is no longer required, patients can take their additional supply to a pharmacy for safe disposal. Disposal of medicines in the household rubbish or by flushing down the toilet is not advised.

In regards to the final question Dr Smith asked, there are many and varied factors as to why rheumatic fever has been largely eliminated from the United Kingdom. It essentially comes down to improved standards of living and better access to healthcare. Rheumatic fever is now most prevalent in developing countries that lack good health infrastructure and where there is overcrowding and poor sanitation. It also affects indigenous communities in countries such as Australia and New Zealand. Rheumatic fever still persists in

low socioeconomic communities in the Northern and Central North Island, and in some parts of the Wellington region, and almost exclusively affects Māori and Pacific peoples in New Zealand.

Is co-trimoxazole an appropriate treatment for cellulitis?

Dear Editor,
Is there a place for using co-trimoxazole in view of increasing resistance to flucloxacillin, as it appears to be equally effective for patients with cellulitis?

Online comment

This question was initially published online in response to a peer group discussion topic based on the article "Cellulitis: skin deep and spreading across New Zealand", BPJ 68 (Aug, 2015).

Response from bpac^{nz} editorial team:
Flucloxacillin has traditionally been the first-line oral antibiotic for patients with cellulitis. Flucloxacillin is a narrow spectrum antibiotic that penetrates skin and soft tissue well. All *Strepococcus pyogene*s and other related streptococci are susceptible to treatment with flucloxacillin, as are approximately 90% of strains of *Staphylococcus aureus* (i.e. all *S. aureus* except for MRSA).[1,2] Co-trimoxazole (trimethoprim + sulfamethoxazole) has poor streptococcal coverage, therefore it is not usually recommended for the empiric treatment of skin infections.[3] Second-line antibiotics for patients with cellulitis include cephalexin, erythromycin and roxithromycin.

Trimethoprim + sulfamethoxazole is best reserved for patients where MRSA is present or suspected, or when antibiotic sensitivities indicate it is an appropriate choice There is a limited choice of oral antibiotics available for the treatment of infections due to MRSA and trimethoprim + sulfamethoxazole should be reserved for this purpose.

There are a number of risks associated with the use of trimethoprim + sulfamethoxazole. It is associated with rare but serious adverse effects, notably blood dyscrasias and Stevens-Johnson syndrome.[4] Trimethoprim + sulfamethoxazole has also been associated with an increased risk of sudden death in older patients also taking spironolactone;[5] this is thought to be due to both medicines causing hyperkalaemia. Trimethoprim + sulfamethoxazole and spironolactone taken concurrently can also result in hyponatraemia. Patients prescribed trimethoprim + sulfamethoxazole are at risk of hyperkalaemia if taking ACE-inhibitors, and at risk of hypoglycaemia if taking sulphonylureas.[4]

In summary, trimethoprim + sulfamethoxazole is not an appropriate first-line empirical treatment for cellulitis in New Zealand, as it has poor streptococcal coverage. It should be reserved for patients with proven antimicrobial sensitivity to trimethoprim + sulfamethoxazole, or for patients with proven or suspected MRSA.

References

1. Clinical Resource Efficiency Support Team (CREST). Guidelines on the management of cellulitis in adults. CREST, 2005. Available from: www.acutemed.co.uk (Accessed Oct, 2015).
2. Thomas MG, Smith AJ, Tilyard M. Rising antimicrobial resistance: a strong reason to reduce excessive antimicrobial consumption in New Zealand. N Z Med J 2014;127(1394):72-84.
3. Bartlett JG. Cellulitis. Johns Hopkins Antibiotic Guide, 2013. Available from: www.hopkinsguides.com (Accessed Oct, 2015).
4. New Zealand Formulary. NZF v40. 2015. Available from: www.nzf.org.nz (Accessed Oct, 2015).
5. Antoniou T, Hollands S, Macdonald EM et al. Trimethoprim-sulfamethoxazole and risk of sudden death among patients taking spironolactone. CMAJ, 2015;187(4):E138-43.

Melatonin in practice

Dear Editor,
In my view the article on Melatonin [Melatonin: Is it worth losing any sleep over? BPJ 69, Aug, 2015] underestimates the true value of this useful agent and I think its importance in human health warrants further discussion. Sleep quality has rightly been described as a central pillar of health.

Assessing the effectiveness of an endogenous biological substance in a randomised controlled trial as if it was a pharmacological agent will always provide a limited perspective simply because its utility probably only relates to deficiency states, and therefore its use is best appreciated when individualised.[1] In short, giving it to patients who do not need it will have little useful effect, and indeed it is often not tolerated. Conversely patients who have difficulty producing melatonin, for whatever reason, are usually

exceedingly grateful for it. Patients who may be struggling to produce sufficient melatonin can usually be identified by giving some consideration to the biosynthesis and physiology of melatonin, and the many extraneous factors that impinge upon it.[2] The key question that assists in identifying the patients that respond has got little to do with how long it took them to fall asleep, but rather by asking them how they felt when they woke up in the morning.

Melatonin is produced by the acetylation and then methylation of 5-hydroxytryptamine (serotonin).[3] Anything that impinges on the biosynthesis of serotonin can potentially find a way to disrupt melatonin biosynthesis. This will include deficiency of substrates and co-factors (such as zinc, magnesium and B6) as well as the regulatory mechanisms that control tryptophan hydroxylase. Add to this anything that disrupts the methylation cycle, also including the availability of its substrates, co-factors, and a number of common gene polymorphisms that alter the activity of enzymes that are rate limiting. A number of single nucleotide polymorphisms influence the function of the melatonin receptors, and these are in turn associated with several disparate disease entities,[2] and are subject to functional deterioration in the context of neurodegenerative disease. Further to this the production of melatonin is subject to two quite pervasive inhibitory factors- light and cortisol!

A corollary of the above in mental health is that a patient with a mood disorder that has responded especially well to an SSRI but still struggles with poor sleep quality, is usually a good candidate for a trial of melatonin, whereas a patient who has not responded well to SSRIs is more likely to dislike its effects.

Melatonin has pleiotropic effects that should cause us to think first of its application to sleep disorders in certain clinical settings, and to consider that melatonin deficiency or receptor dysfunction may have consequences "which go far beyond sleep difficulties." [2] Melatonin has been widely researched in the context of cancer (there are 1897 papers currently referenced in PubMed),[4, 5] and there are now five known mechanisms for its potential supportive role in cancer treatment, the most widely known being its ability to up-regulate Natural Killer Cell activity.

Its reputation as the most powerful anti-oxidant capable of passing the blood-brain barrier suggests a role for it in sleep disorders in the context of neurodegenerative diseases of the ageing brain. Age-related decline in melatonin production is of course a striking feature of its physiology. Melatonin is especially clever in its antioxidant capacity as it achieves this not by actually being an antioxidant itself, but by up regulating endogenous cellular antioxidant defences (the same way that broccoli does!), by activating the ARE-NrF2 transcription complex.[6–9] A recent discovery has been the efficacy of melatonin in restoring normal night time "dipping" of blood pressure in hypertensive patients, who are at especially high risk of end organ damage when the dysregulation of blood pressure has this attribute.[10–15] A protective role in metabolic syndrome has also recently been explored.[16] Sleep disorders in the context of chronic inflammation are also candidates for a trial of melatonin, as certain inflammatory cytokines will upregulate the enzyme IDO, shifting tryptophan metabolism away from the production of serotonin/melatonin, and instead diverting it to an alternate biochemical pathway that can further exacerbate neural inflammation.[17] Sleep problems associated with neurodevelopmental disorders such as autism is another area in which melatonin has demonstrated well established benefits.[18,19]

Whilst there are rightly concerns about the lack of long-term studies on the effects of melatonin , it can at least be said that there are no patients who suffer from benzodiazepine (or other hypnotic drug) deficiency. The benzodiazepines (and probably related drugs) cause down regulation of the GABA receptor, their long term use is linked with cognitive deficits that are not fully recoverable with discontinuation of the drug, and they are associated with an increased incidence of dementia and even mortality.[20–23] They are truly substances of last resort, yet continue to be widely used. That is something to lose sleep over!

Dr William Ferguson, *General Practitioner*
Kumeu

Reference list available from: **www.bpac.org.nz/BPJ/2015/October/correspondence.aspx**

We value your feedback. Write to us at: Correspondence, PO Box 6032, Dunedin or email: editor@bpac.org.nz