RGH E-Bulletin Digest Number 82

The next in our 2015 series of continuing professional development activities is the RGH E-Bulletin Digest No. 82 – edited by Associate Professor Chris Alderman.

This CPD activity assesses your understanding of four recent RGH Pharmacy E-Bulletins, Volumes 57-12→58-3 (March/April 2015).

Learning Objectives:

After completing this activity, pharmacists should be able to:

- Describe the latest views about treatment of male-gender urinary tract infections
- Discuss the treatment of vitamin B12 deficiency
- Outline issues in contraceptive selection for women with known risk factors
- Demonstrate understanding of issues relating to the use of dosage administration aids (DAAs).

Information in this E-Bulletin Digest is derived from critical analysis of available evidence – individual clinical circumstances should be considered when making treatment decisions.

Competencies addressed by this activity include: 4.1, 4.2, 4.3, 6.1, 6.2, 7.1, 7.2.

Successful completion of this activity is demonstrated by answering seven of the eight multiple choice questions correctly.

This activity has been accredited for 0.5 hrs of Group 1 CPD (or 0.5 CPD credits) suitable for inclusion in an individual pharmacist's CPD plan which can be converted to 1 hr of Group 2 CPD (or 1 CPD credit) upon successful completion of relevant assessment activities.
Accreditation number: A1507AP0.

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He is a past president of the Society of Hospital Pharmacists of Australia and achieved admission as a Fellow of SHPA in 1993. He is the author of over 80 peer-reviewed publications and several book chapters, and his research interests focus upon strategies to achieve safe and effective use of psychotropic drugs. He has a special interest in veteran psychiatry, in particular in the management of post-traumatic stress disorder.

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RGH Pharmacy E-Bulletin

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A joint initiative of the Patient Services Section and the Drug and Therapeutics Information Service of the Pharmacy Department, Repatriation General Hospital, Daw Park, South Australia. The RGH Pharmacy E-Bulletin is distributed in electronic format on a weekly basis, and aims to present concise, factual information on issues of current interest in therapeutics, drug safety and cost-effective use of medications.
Editor: Assoc. Prof. Chris Alderman, University of South Australia – Director of Pharmacy, RGH

Male gender and urinary tract infection treatment

Choosing the correct duration of antibiotic treatment is important - not only for optimal treatment of infection, but also to minimise risk of *Clostridium difficile* super-infection, side effects, antibiotic resistance and cost of treatment. Recently, further evidence has resulted in an update in the guidelines for treatment duration of cystitis in males. The new recommendation published in the Australian Therapeutic Guidelines is to treat for 7 days rather than 14 days (as was the case in the previous 2010 guidelines). This change was based on the outcomes of a study published in the Journal of the American Medical Association in 2013.

Prior evidence from a study of patients with spinal cord injury supports treatment for 14 days rather 3 days; and treatment for 14 days over 28 days in males with febrile UTI. The current JAMA study was conducted with the aim of determining whether there is any benefit from treating UTIs in men for duration of greater than 7 days, versus less than 7 days. Outpatient electronic medical records from Minneapolis Veterans Health administrative facilities were searched to identify cases of male UTI associated with an antibiotic prescription. 39 149 cases of UTI, as diagnosed according to the International Classification of Diseases, were identified and were subdivided into several classes: the patient's first UTI in the year of data collection, an early recurrence (<30 days), or a late recurrence (≥ 30 days).

Of these patients with an initial UTI episode, 4.1% had an early recurrence and 1.7% had a late recurrence. The rate of early recurrence was similar between patients treated with short and long durations of antibiotics (3.9% for ≤ 7 days vs 4.2% >7 days, p = 0.16). Similarly, the risk of late recurrence was not reduced by using a long duration compared with a short duration of antibiotics. In fact, there was an increase in late recurrence with a longer duration of therapy. Another important result was that in the short duration group most of the patients (77%) were treated for 7 days, where as in the long duration group most were treated for 10 days (66%), so the actual difference in treatment duration between the groups was relatively small.

This study also recorded cases of *C. difficile* infection and, as expected, the results suggested that a longer duration of therapy was associated with a significant increase in infection (0.5% vs 0.3%, p = 0.02). Unfortunately, other antimicrobial use was not recorded and this may have influenced the risk of *C. difficile* infection.

The authors acknowledged that a larger proportion of patients with an increased risk of recurrence may have been represented in the group receiving a longer duration of treatment. The study assessed drug treatment, treatment duration, and outcomes (recurrence and Clostridium difficile infection during 12 months), as well as demographic, clinical, and treatment characteristics, assessing associations with outcomes in univariate and multivariate analyses. However one important risk factor that was not able to be recorded was catheter use. Another limitation to this study was the uncertainty in diagnosis of UTIs through identification of cases using the ICD codes, and no ability to determine whether or not the UTI was symptomatic.

Optimally current guidelines would be based upon on data from randomized controlled trials, which would help to minimize sources of bias. However in the current absence of this type of data, this observational study provides some evidence to further guide the optimal treatment duration of UTIs amongst male patients. Along with the change in recommendations for treatment duration, the current Australian guidelines also emphasize the importance of performing thorough investigations in males presenting with a UTI, in order to identify patients with complications such as prostatitis, which would necessitate a longer duration of treatment.

Acknowledgment – This E-Bulletin is based on work by Heather Forbes, Senior Clinical Pharmacist, RGH

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RGH Pharmacy E-Bulletin

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An overview of dose administration aids

Dose Administration Aids (DAAs) are adherence devices for solid-dose medications (e.g. tablets and capsules). Medications are organised into individual doses and arranged according to dosing times throughout the day (e.g. breakfast, lunch, dinner, bed). DAAs may be tamper-evident (sealed) or non-tamper evident (reusable). The most commonly used DAAs include:

Sealed bubble packs
Examples include Webster-Pak, MedicoPak. These are disposable cardboard/plastic devices with one week of medications per pack, divided into four dose times. They are most commonly prepared by community pharmacies, and generally a fee is charged for this service.
Reusable boxes
These include Dosette® boxes. These are available in many variations, including one, two or four dose times per day. As they are reusable, they are often packed by consumers or carers, but can also be prepared by pharmacies.
Sachets
Such as APHS Medisachets.®These are packed by automated packing systems, with pharmacies often outsourcing packing to larger companies. Each sealed sachet contains medications for a single dosing time (e.g. 8AM), and the sachets are chronologically arranged on a long roll. This system is often utilised for Residential Care Facility residents.

Advantages of DAAs include convenience, improved adherence, reduced medication mismanagement and simplified medication administration system for carers and facility staff. While DAAs can be a valuable aid to improve adherence in some consumers, they do have disadvantages and are not a blanket solution for all adherence problems:

- Consumer loss of knowledge and/or independence with medication management
- Lack of evidence regarding medication stability in DAAs
- Some solid dosage medications inappropriate for DAAs
- Potential dexterity or coordination issues removing medications from DAAs
- Potential for delays and errors with frequent medication changes and transitions between care episodes
- Costs associated with pharmacy-packed DAA service

The stability of medications packed in DAAs is unclear, with little evidence available about removing medications from original packaging. In Australia, few medications have been specifically studied for stability when packed into DAAs, leaving pharmacists to make individual judgements on suitability. Furthermore, several types of medications are known to be inappropriate to pack into DAAs, such as effervescent or soluble tablets, sublingual tablets, hygroscopic or moisture-sensitive medications (sodium valproate, dabigatran) and light-sensitive tablets (nifedipine). Some refrigerated tablets (e.g. thyroxine) are only stable for a short time packed at room temperature. Before recommending a DAA system for a consumer, many factors must be assessed. Firstly, other options to improve adherence should be considered, such as a medication list, reminder chart or diary. DAA option should be carefully discussed with the consumer, including any costs involved. The consumer's understanding of the DAA system & ability to use it accurately should be assessed, and their medications reviewed for packing suitability. Up-to-date records and good communication between the pharmacy, GP & consumer must be maintained. Resources available regarding DAAs include:

Pharmacy Board of Australia "Guidelines on specialised supply arrangements" http://www.pharmacyboard.gov.au/Codes-Guidelines.aspx

Pharmaceutical Society of Australia "Dose Administration Aids Service" http://www.psa.org.au/supporting-practice/professional-practice-standards/dose-administration-aids-service

Acknowledgment – This E-Bulletin is based on work by Eleanor Kelly, Senior Clinical Pharmacist, RGH

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Medical eligibility criteria for contraceptive use

Most patients who use contraceptives are medically fit and are able to safely use any method of contraception. However, in clinical practice, medical practitioners may be presented with the question of whether a particular type of contraception would be suitable for a patient with a known medical condition.

Some medical conditions may be associated with theoretical increased health risks when certain contraceptives are used. In 2009, the World Health Organization (WHO) published the fourth edition of the "Medical eligibility criteria for contraceptive use" (http://whqlibdoc.who.int/publications/2010/9789241563888_eng.pdf?ua=1), with the aim that the recommendations would be updated every three to four years. The Faculty of Sexual and Reproductive Healthcare in the United Kingdom (UK) published a similar document in 2009 called the "UK Medical Eligibility Criteria for Contraceptive Use" (http://www.fsrh.org/pdfs/UKMEC2009.pdf). The recommendations in the "Contraception: an Australian clinical practice handbook" (third edition) are based on the UK recommendations.

The WHO and UK documents review the medical eligibility criteria (MEC) for the different contraceptive methods that are available for patients with specific characteristics or known medical conditions. The recommendations are based on systematic reviews of available clinical and epidemiological research, and are to be used as a guide for the safe use of contraceptives. They should not replace clinical judgement and evaluation in individual patient situations. There are four MEC categories:

1. A condition for which there is no restriction for the use of the contraceptive method.
2. A condition where the advantages of the method generally outweigh the theoretical or proven risks.
3. A condition where the theoretical or proven risks usually outweigh the advantages of using the method.
4. A condition which represents an unacceptable health risk if the contraceptive method is used.

These principles are illustrated below in an example of a patient with a known thrombogenic mutation (e.g. protein S deficiency). Using the WHO recommendations and considering preparations that are available in Australia, combined oral contraceptives (COCs) and the combined contraceptive vaginal ring have a MEC category 4 rating, (as one study showed that in women with thrombogenic mutations, COC users had a 2–20 fold higher risk of thrombosis than in non-COC users). The progestogen only pills, the etonogestrel implant, depot medroxyprogresterone acetate and the levonorgestrel-releasing intra-uterine device (IUD) have a MEC category 2, suggesting that one of these could be considered as an option once clinical judgement and patient preference is taken into account. The copper-releasing IUD and barrier methods of contraception have a MEC category 1 suggesting that these could be used safely in a patient with a known thrombogenic mutation once clinical judgement and patient preference is considered. For further information please refer to:

WHO Medical eligibility criteria for contraceptive use, 2009, 4th edition
http://whqlibdoc.who.int/publications/2010/9789241563888_eng.pdf?ua=1

UK Medical Eligibility Criteria for Contraceptive Use, 2009, 2nd edition
http://www.fsrh.org/pdfs/UKMEC2009.pdf

Sexual Health and Family Planning Australia. Contraception: an Australian clinical practice handbook. 3rd ed. ACT: Sexual Health and Family Planning Australia, 2012.

Acknowledgment – This E-Bulletin is based on work by Eleanor Kelly, Senior Clinical Pharmacist, RGH

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Editor: Assoc. Prof. Chris Alderman, University of South Australia – Director of Pharmacy, RGH

Vitamin B12 deficiency

Vitamin B12, also referred to as cobalamin, is an essential cofactor in DNA synthesis and cellular metabolism, including haematopoiesis. Vitamin B12 also has important role in sustaining myelin in the nervous system. Intracellular conversion of vitamin B12 produces active coenzymes, adenosylcobalamin in mitochondria and methylcobalamin in the cytoplasm – these are essential for homeostasis of methylmalonic acid (MMA) and homocysteine. Vitamin B12 deficiency is common, with an increased incidence amongst the elderly, during pregnancy, or with impaired GIT absorption, poor nutrition and strict vegan or vegetarian diets. Dietary sources of vitamin B12 are only found in animal products, including lean meats, seafood chicken, eggs offal and milk. Presence of intrinsic factor is required for adequate intestinal absorption. Specific causes of deficiency include autoimmune gastritis, gastric and/or ileum resection, pernicious anaemia, pancreatic insufficiency, malabsorption syndromes, intrinsic factor inadequacy, dietary insufficiency, chronic alcohol abuse, intestinal bacterial overgrowth or parasitic infections. The use of some medications, including metformin, Proton Pump Inhibitors (PPIs), H2 Antagonists, colchicine, and potassium is also associated with B12 deficiency.

Clinical presentation is often obscure, with diverse signs that vary in accordance with severity and underlying cause. Mild clinical features include fatigue and taste impairment, but neurological signs are usually not present. Moderate deficiency is associated with dyspnoea, palpitations, pallor & macrocytic anaemia, as well as glossitis, skin hyperpigmentation and subtle neurological signs such as sensory impairment, peripheral neuropathy, paraesthesia, loss of proprioception, depression & cognitive changes. Severe clinical features include profound megaloblastic anaemia, obvious neurological deficits (such as myelopathy, sensory loss, ataxia, spasticity or hyporeflexia, significant cognitive impairment, optic nerve atrophy, autonomic dysfunction, psychosis/delusions). Other syndromes associated with severe deficiency include bone marrow suppression, osteoporosis & increased fracture risk, & increased risk of cardiomyopathy.

No single test is ideal for measuring vitamin B12 deficiency, with total serum vitamin B12 (serum cobalamin) remaining the study of choice, used in combination with red blood cell parameters and peripheral smear. Serum B12 is not highly specific (due to protein binding) but consensus suggests that deficiency would be regarded as a serum concentration < 148pmol/L (<200ng/L). Additional investigations to assess the biologically active and inactive functionality of B12 include measurement of serum holotranscobalamin (active B12, a measure of transcobalamin-bound vitamin B12 - only this form is metabolically active and available for cellular uptake). In some cases measurement of intrinsic factor & antiparietal cell antibodies are also used. Screening for vitamin B12 deficiency is currently not recommended due to poor sensitivity of assays and associated costs. In all cases clinical examination remains of greatest importance.

Timely treatment is important, especially in severe cases, to prevent bone marrow deficits, thrombotic risk (due to elevated homocysteine) & irreversible neurological damage. IM hydroxocobalamin remains standard first line treatment due to long bodily retention. Recommended total dosing is between 3 - 10 mg over the course of 2 - 4 weeks. Severe deficiency with potentially irreversible outcomes requires prompt replacement at higher doses of 1 mg IM alternate daily for 14 - 20 days. Milder deficiency, or those without anaemia or neurological presentation, can be managed with 1mg IM twice/thrice weekly for two weeks. Oral cyanocobalamin may be an option in circumstances where IM injections aren't tolerated, but high doses are required for equivalent results. Oral preparations should be avoided in severe deficiency & malabsorption causes. Following initial IM dosing, fatigue and malaise can improve within 24-48 hours. Haematological assessment of response occurs within days, with complete response within two months. Neuropathy is slow to improve and residual deficits may persist. Serum vitamin B12 and holotranscobalamin are not reliable indicators of response to treatment; however MMA and homocysteine usually normalize within 1-2 weeks. Maintenance supplementation will generally be required for life, with suitable dosing of 1mg IM every 2 - 3 months, unless deficiency cause is reversible.

Acknowledgment – This E-Bulletin is based on work by Lauren Wierenga, Senior Clinical Pharmacist, RGH

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References used in the preparation of the relevant E-Bulletins:

Elliott, RA. 2014 Appropriate Use of Dose Administration Aids, Australian Pharmacist, 37, 46 – 50

Haywood A, Llewelyn V, Robertson S, Mylrea M, Glass BD. 2011 Dose Administration Aids: Pharmacists' role in improving patient care, AMJ 4,4, 186 – 192

Pharmaceutical Society of Australia "Dose Administration Aids Service" www.psa.org.au/supporting-practice/professional-practice-standards/dose-administration-aids-service

Hunt, A et al. 2014. Clinical Review: Vitamin B12 deficiency. BMJ.

Sobczynska-Malefora, A, et al. 2014. An audit of holotranscobalamin and methylmalonic acid assays for the assessment of vitamin B12 status: application in a mixed patient population. Clinical Biochemistry.

Heil, SG, et al. 2012. Screening for metabolic vitamin B12 deficiency by holotranscobalamin in patients suspected of vitamin B12 deficiency: a multicenter study. Annals of clinical biochemistry.

Valenta, E, et al. 2011. Diagnostic accuracy of holotranscobalamin, methylmalonic acid, serum cobalamin, and other indicators of tissue vitamin B12 status in the elderly. Clinical Chemistry

Aisari, F, et al. 2010. Comparison between serum holotranscobalamin and total vitamin B12 as indicators of vitamin B12 status. Oman Medical Journal

WHO Medical eligibility criteria for contraceptive use, 2009, 4th edition (whqlibdoc.who.int/publications/2010/9789241563888_eng.pdf?ua=1

UK Medical Eligibility Criteria for Contraceptive Use, 2009, 2nd edition www.fsrh.org/pdfs/UKMEC2009.pdf

Sexual Health and Family Planning Australia. Contraception: an Australian clinical practice handbook. 3rd ed. ACT: Sexual Health and Family Planning Australia, 2012.

Drekonja DM, Rector TS, Cutting A, Johnson JR. Urinary Tract Infection in Male Veterans: Treatment Patterns and Outcomes. JAMA Intern Med. 2013;173:62-68

Trautner BW. New Perspectives on Urinary Tract Infection in Men. JAMA Intern Med. 2013;173:68-69

Becky A. Smith, MD, Lance R. Peterson, MD. (2013, March 04). Treating Urinary Tract Infections in Men: Primum non nocere. Medscape. Retrieved 09/03/2015 from http://www.medscape.com/viewarticle/779530

Urinary Tract Infections [revised 2014 Oct]. In: eTG complete [Internet]. Melbourne: Therapeutic Guidelines Limited; 2014 Oct.

AusPharm CPD MCQs

Questions based on the above articles:

Successful completion of this activity is demonstrated by answering seven of the eight multiple choice questions correctly.

Select ONE alternative that best represents the correct answer to each of the following multiple choice questions

The new recommendation published in the Australian Therapeutic Guidelines is to treat cystitis in males for:

a) 3 days
b) 7 days
c) 14 days
d) 21 days

Recent research suggests that when compared to extended treatment with antibiotics for male-gender UTIs, briefer treatment was associated with:

a) less recuurences
b) more recurrences
c) less clostridium difficile diarrhoea
d) more clostridium difficile diarrhoea

Which of the flowing drugs may be unsuitable for packing in a Dose Administration Aid (DAA):

a) clopidogrel
b) warfarin
c) dabigatran
d) rivaroxaban

Which of the following is an example of a tamper-evident DAA?

a) sachet packing prepared in a pharmacy
b) a Dosette® box
c) day organiser medication box
d) none of these

An example of a known thrombogenic mutation is:

a) protein S deficiency
b) alteplase inhibition
c) vitamin K deficiency
d) all of the above

Which contraception would be regarded as the least hazardous for a woman with a known thrombogenic mutation?

a) combined oral contraceptive
b) combination vaginal ring
c) levonorgestrel-releasing intra-uterine device IUD
d) copper-releasing IUD

Specific causes of vitamin B12 deficiency include

a) autoimmune gastritis
b) pancreatic insufficiency
c) intrinsic factor inadequacy
d) all of the above

The suggested treatment regimen for severe vitamin B12 deficiency is:

a) 1 mg IM B12 alternate daily for 14 - 20 days
b) 1 mg B12 IM daily for 14 - 20 days
c) 0.1 mg B12 IM alternate daily for 14 - 20 days
d) 0.1 mg B12IM daily for 14 - 20 days