



# BREAK POINT

## 2013 - ISSUE 01

### WELCOME TO THE FIRST NEWS SHEET OF THE SOCIETY FOR 2013

Welcome to the first edition of “Breakpoint”, ASA’s new look news sheet. For this year, ASA has increased the frequency of the newsletter to bi-monthly, however, to facilitate reading and access to content, there will be a single main article. In this issue, Lucy White, from the Department of Pharmacy, Westmead Hospital, provides an update of the status of fidoxamicin in the treatment of *Clostridium difficile* diarrhea. To begin with, there will also be one or more [newsworthy items](#) of interest either from the media and/or the literature. Readers are welcome to submit any items of this nature! As ASA will be introducing the “Howard Florey” plenary in future annual scientific meetings, it is fitting to revisit the contribution of this great scientist to antimicrobial development. Please see the short article by John Turnidge.

The [picture quiz](#) and the [conference calendar](#) follow. Feedback regarding Breakpoint and the new format is most welcome.

All the best

**Sharon Chen**  
ASA News sheet Editor





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## NEWS: NOVEL ANTI-TUBERCULOSIS DRUG?

WHO have reported an estimated 310,000 cases of multi-drug resistant tuberculosis in 2011. Bedaquiline, a diarylquinoline, targets mycobacterial adenosine triphosphate synthase as opposed to the quinolones that target DNA gyrase, and is cidal for *M. tuberculosis*. Data from 2 midstage trials indicate that when added to standard therapy for multi-drug resistant TB, it reduces the time to conversion to a negative sputum culture. We await the results of stage 3 trials with interest. In September 2012, the FDA granted priority review of this medicine. Watch this space!

*Read: Diacon et al. The diarylquinoline TMC207 for multi-drug resistant tuberculosis. N Engl J Med 2009; 360: 2397-2405.*

## HOWARD FLOREY ORATION

Howard Walter Florey (1898-1968), although not the first to recognise the possibilities of antibiosis, was, through a wonderful combination of skill, luck and teamwork, able to turn a laboratory curiosity—described by Alexander Fleming in 1929—into the first ‘miracle drug’. Born in the suburb of Malvern in Adelaide, while Australia was still a collection of British colonies, his academic prowess was recognised while attending high school at St. Peter’s College. He studied medicine at the University of Adelaide and then, like so many talented Australians at the time, in 1922 sought further training in the ‘mother country’. Going from strength to strength in England, Florey established his career at the William Dunn



<http://www.adelaide.edu.au/lifeimpact/stories/millions-saved.html>

School of Pathology at Oxford University. Here he became interested in antibiosis and started his antibiotic research looking at lysozyme. However, exploring the possibility that Fleming’s ‘discovery’ might also be a good antibiotic, he gathered a team with diverse skills and took the bold steps to prove the true selective toxicity of penicillin. Ironically, the greatest boost to turning his research into everyday patient treatment was the Second World War. The US in particular recognised the therapeutic potential of penicillin in managing wound infections, at a time when the United Kingdom was devoting all its resources to the war effort. Indeed it required Florey and other team members to go to the US during WWII to get the scaled-up manufacturing required for production of penicillin as treatment, a far cry from culturing *Penicillium* in endless numbers of bedpans, as they were forced to do in Oxford. Together with Fleming and Ernst Chain, all this work eventually led to the awarding of a Nobel Prize in Physiology and Medicine in 1945. Florey went on to do research into atherosclerosis and lymphatics, but never forgot antibiotics and worked with isoniazid, streptomycin, nisin, micrococin, cephalosporins P1, proactinomycins and other antibiotics (check out PubMed “Florey HW”). At least one of his biographies suggested that later in life he suffered chronic dyspepsia. Could this have been *Helicobacter* infection, another discovery by Australians that earned a Nobel Prize in Medicine? Florey finally returned to Australia in 1965 as the inaugural Chancellor of the Australian National University in Canberra, the same year as he was made a life peer as Baron Florey of Adelaide. In one of his most telling quotes, he stated in his usual laconic way: “Developing penicillin was a team effort, as these things tend to be.” We hope his spirit lives on.

**John Turnidge**

*Women’s and Children’s Hospital, Adelaide*



## FIDAXOMICIN: NEW TREATMENT FOR CLOSTRIDIUM DIFFICILE INFECTION

Lucy White, Antimicrobial Stewardship Pharmacist, Westmead Hospital, Sydney

### Background

Over the past decade, the commonest cause of both health care-associated and antibiotic-associated diarrhoea, *Clostridium difficile*, has become of increasing concern. The extent of this burden has risen primarily from the emergence of hyper virulent strains (for example, PCR ribotype 027), which have been associated with increasing severity, as well as mortality due to infection. Furthermore, a reduced response rate to, and a high relapse rate after standard therapies such as oral metronidazole and/or oral vancomycin have led to heightened concern for health care institutions.

New therapies to treat *Clostridium. difficile* infection have been developed. Fidaxomicin (Dificid™, Optimer Pharmaceuticals) is one such drug which show promise as an anti-*Clostridium. difficile* agent. In Australia, fidaxomicin is not yet registered and needs to be acquired via the Special Access Scheme (SAS). However, an application for registration has been submitted to the Therapeutic Goods Administration, and is anticipated to launch by mid-2013.

### Characteristics and *in vitro* activity

Fidaxomicin is a locally-acting macrolide antibiotic which exerts its bactericidal effect via protein inhibition of the RNA polymerase enzyme. It is notable for its narrow spectrum of activity with primary action limited against *Clostridium species*. Some reports estimate that it is up to eight times more active *in vitro* than vancomycin against clinical isolates of *Clostridium. difficile*, including the hyper virulent strains.

Fidaxomicin has been shown to achieve very high faecal concentrations which are suitable for the treatment of *Clostridium difficile*-associated diarrhoea (CDAD). The agent demonstrates minimal systemic absorption, which renders it clinically ineffective in treating any systemic infection. In May 2011 it was approved by the United States Food and Drug Administration for the treatment of CDAD in adults. In December 2011, it was also approved in Europe for the same indication.

### Dosing schedule

The current dosage recommendation for adults is 200mg orally twice daily for a total of ten days. Fidaxomicin is metabolised to the OP-1118 metabolite via hydrolysis of the isobutyryl ester primarily in the intestine and does not depend on CYP450 enzymes. Up to 92% is then excreted in the faeces (changed and unchanged) with 0.59% being excreted renally. Therefore, current information suggests that dose adjustment is not required for gender, increasing age, or declining renal/hepatic function. The safety and efficacy of this product in paediatric patients is yet to be established and therefore not recommended for use. Following oral administration, fidaxomicin has demonstrated a post-antibiotic effect against *Clostridium difficile* of up to 12.5 hours, compared to up to 1.5 hours for oral vancomycin. This is believed to contribute to the efficacy of fidaxomicin in the treatment of CDAD.

### Efficacy in CDAD

Fidaxomicin has been evaluated in 2 large double-blind randomized non-inferiority trials. The first trial showed fidaxomicin to be non-inferior to oral vancomycin for cure in 629 participants, with significantly lower recurrence rates than oral vancomycin for non-NAP1/BI/027 strains. The second trial investigated 535 patients and has reported similar results. Furthermore, the narrow-spectrum, bactericidal nature of fidaxomicin may provide an added benefit over an agent such as vancomycin which is broader-spectrum and bacteriostatic.



## FIDAXOMICIN: NEW TREATMENT FOR CLOSTRIDIUM DIFFICILE INFECTION CONT'D

Lucy White, Antimicrobial Stewardship Pharmacist, Westmead Hospital, Sydney

### Adverse effects

Although fidaxomicin does not list any contraindications to its use, there are some notable adverse effects which should be considered before starting therapy, including (but not limited to):

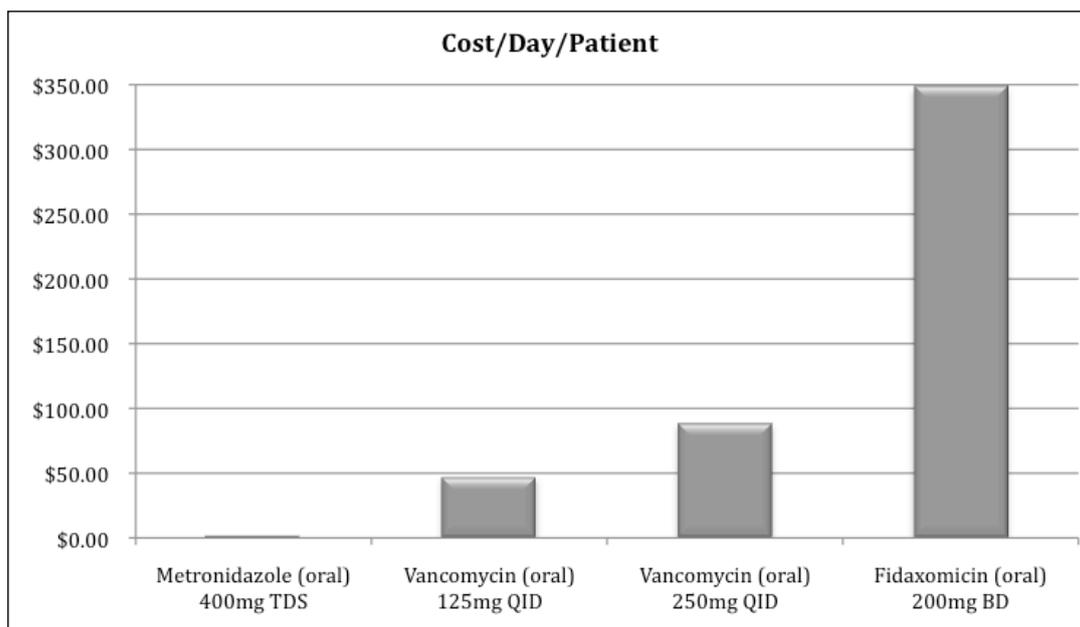
- Gastrointestinal
- Abdominal pain (6% )<sup>\*^</sup>, Nausea (11% )<sup>\*^</sup>, Vomiting (7% )<sup>\*^</sup>, Gastrointestinal haemorrhage (4% )
- Haematologic
- Anaemia (2% ), Neutropenia (2% )<sup>\*^</sup>
- Dermatologic
- Rash and Pruritis (less than 2% )<sup>\*^</sup>

It should be noted, that oral vancomycin\* and oral metronidazole<sup>^</sup> also list a range of possible adverse effects including some of those listed above (note: incidence listed is for fidaxomicin and does vary between the different drugs).

### Comparative costs

The cost of acquisition of the three treatment options for Clostridium difficile infection is likely to vary between institutions; however figure 1 demonstrates an estimation of current costs for approximate comparison:

Figure 1: Cost comparison of CDAD treatment options



In summary, the qualities of fidaxomicin such as it being bactericidal, having a narrow spectrum and demonstrating lower recurrence rates than standard therapies have made it an attractive option for the treatment of CDAD. However, due to its lack of superiority in trials, current SAS status in Australia and remarkably high cost compared to standard therapies, its use in the treatment of CDAD is often limited to being a third line option.

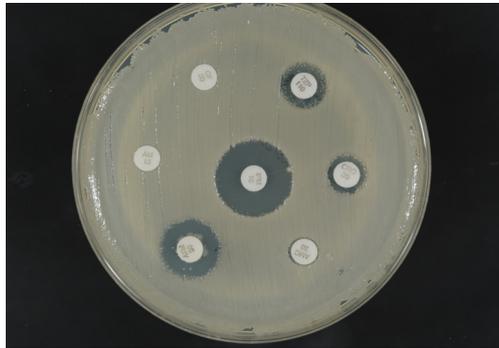
## PICTURE QUIZ - QUESTION

Koh Tse Hsien, Singapore General Hospital, Singapore

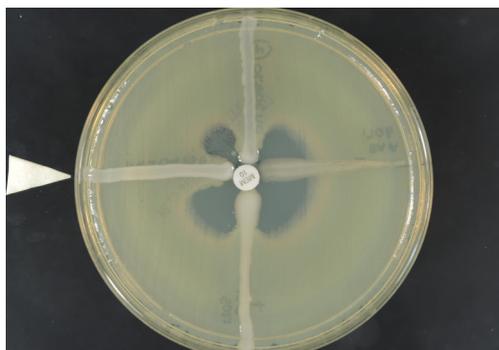
A *Klebsiella pneumoniae* was isolated from the urine of a 72 year old Chinese lady in a nursing home in Singapore. She had no recent travel history. The zone of inhibition around the imipenem disk was 19 mm (resistant). The imipenem MIC was 4 mg/L by Etest. The results of the other antimicrobial susceptibility tests are shown in Figures 1-3.

What is the likely mechanism of carbapenem resistance?

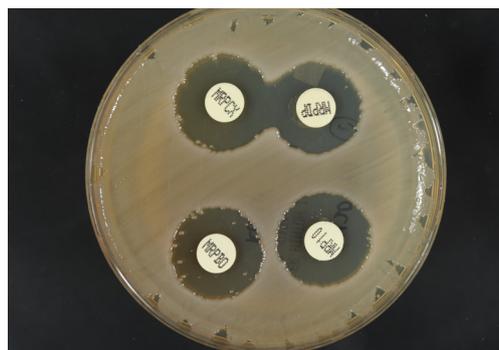
**Figure 1.** Antimicrobials clockwise from top right; piperacillin-tazobactam, ceftriaxone, amoxicillin-clavulanate, aztreonam, ampicillin, cephalothin, imipenem (center).



**Figure 2.** Modified Hodge test with arrow pointing at test isolate.



**Figure 3.** Rosco KPC+MBL kit. Clockwise from bottom right; meropenem, meropenem and boronic acid, meropenem and cloxacillin, meropenem and dipicolinic acid.

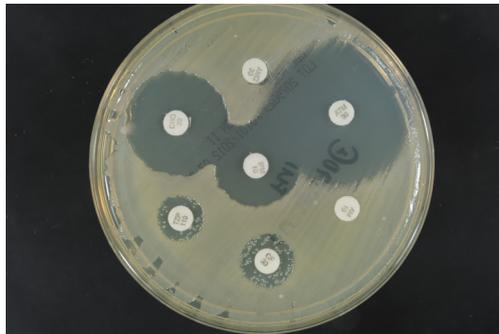


## PICTURE QUIZ - ANSWER

A second isolate from the same urine sample had large zones of inhibition around the ceftriaxone and aztreonam disks (Figure 4). The imipenem disk diameter was 22mm (susceptible). The imipenem MIC for the second isolate was 1 mg/L by Etest.

Both isolates had the same modified Hodge test and Rosco KPC+MBL kit result and pulsed-field gel electrophoresis pattern. Isolate 1 was positive for a CTX-M group 1 extended-spectrum- $\beta$ -lactamase gene whereas isolate 2 was negative. Both isolates were positive for an OXA-48 carbapenemase gene confirmed by DNA sequencing.

**Figure 4.** Antimicrobials clockwise from bottom left; piperacillin-tazobactam, ceftriaxone, amoxicillin-clavulanate, aztreonem, ampicillin, cephalothin, imipenem (center).



The OXA-48 carbapenemase was first described in a *K. pneumoniae* isolate from Turkey in 2004 (1). OXA-48 producing Enterobacteriaceae have since caused outbreaks in that country and spread to other parts of Europe and Africa. A related enzyme, OXA-181, has been found in the Indian subcontinent and is also starting to spread (2).

By themselves, OXA-48 and OXA-181 hydrolyze carbapenems weakly and spare the third generation cephalosporins (as seen in the second isolate). However this characteristic antibiogram may be obscured by the presence of another  $\beta$ -lactamase as in the case of the first isolate.

*Patrice Nordmann an antimicrobial resistance expert from France has identified the OXA-48 family of carbapenemases as being particularly difficult to detect and identify. They should be suspected in the presence of a strong modified Hodge test result and a negative Rosco KPC+MBL test. ROSCO have recently incorporated temocillin into their kit as OXA-48 producing Enterobacteriaceae are highly resistant to temocillin.*

1. Poirel L, Héritier C, Tolün V, Nordmann P. Emergence of oxacillinase-mediated resistance to imipenem in *Klebsiella pneumoniae*. *Antimicrob Agents Chemother.* 2004 Jan;48(1):15-22.

2. Castanheira M, Deshpande LM, Mathai D, Bell JM, Jones RN, Mendes RE. Early dissemination of NDM-1- and OXA-181-producing Enterobacteriaceae in Indian hospitals: report from the SENTRY Antimicrobial Surveillance Program, 2006-2007. *Antimicrob Agents Chemother.* 2011 Mar;55(3):1274-8.



## 2013 MEETING CALENDAR

### **Pathology Update: Melbourne under the Microscope**

22-24 February, Melbourne, Victoria

Website: <http://www.rcpa.edu.au>

### **Australian Society for Antimicrobials Annual Meeting**

February 21-23, Sydney, NSW

Website: [www.asainc.net.au/](http://www.asainc.net.au/)

### **Molecular Biology Meeting**

March 6-7, Waterview Convention Centre, Sydney Olympic Park, NSW

Website: [www.mmm.mtci.com.au/](http://www.mmm.mtci.com.au/)

### **9<sup>th</sup> International Symposium on Antimicrobial Agents and Resistance**

March 13-15, Kuala Lumpur, Malaysia

Website: <http://www.isaar.org>

### **Australasian Society for Infectious Diseases Annual Meeting**

March 20-23, Canberra, ACT

Website: [www.asid.net.au/](http://www.asid.net.au/)

### **23<sup>rd</sup> European Congress of Clinical Microbiology and Infectious Diseases (ECCMID)**

27 – 30 April, 2013, Berlin, Germany

website: <http://www.escmid.org>

### **American Society for Microbiology Annual Meeting**

28-31 May, Denver, Colorado

Website: [www.asm.org](http://www.asm.org)

### **28<sup>th</sup> International Congress of Chemotherapy and Infection**

5-8 June, Yokohama, Japan

Website: <http://www2.convention.co.jp/icc2013/>

### **Australian Society for Microbiology Annual meeting**

7-10 July, Adelaide, South Australia

Website: [www.theasm.org.au](http://www.theasm.org.au)

### **52<sup>nd</sup> Interscience Conference for Antimicrobial Agents and Chemotherapy**

Sept 10-13, Denver, Colorado

Website: [www.icaac.org/](http://www.icaac.org/)

### **ID week (IDSA, SHEA, HIVMA, PIDS)**

Oct 2-6, San Francisco, California

Website: <http://www.idweek.org/idweek2013>