The first drug in a new class of antibiotics know as the glycylcyclines has been launched in the UK, which will provide a new treatment option for drug-resistant bacterial infections, including important hospital-acquired pathogens.

New 'superbug' drug, Tygacil® launched in the UK

A new, broad-spectrum intravenous antibiotic, Tygacil® (tigecycline), was launched in the UK at the end of July. The drug, which is the first in a new class of antibiotics known as glycylcyclines, is an expanded, broad-spectrum antibiotic which is available for the treatment of a variety of infections including some caused by antibiotic-resistant bacteria.

The drug, which has been developed by pharmaceutical company, Wyeth, represents an important addition to the physician's drug armamentarium against infections that are becoming increasingly difficult to treat effectively.

The drug is currently licensed to treat complicated skin and skin structure infections, in addition to complicated intra-abdominal infections. After being licensed for use by the European Commission in Europe on April 24th, the drug became available in the UK on July 20th.

Robert Masterton, Executive Medical Director and Consultant Microbiologist for the UK National Health Service (NHS, Ayrshire and Arran, UK) commented that "Difficult-to-treat, antibiotic-resistant and often life-threatening infections are a growing problem in the UK, costing the National Health Service an estimated additional £1 billion annually," He continued that "Even more worrying has been the emergence of the organisms commonly called 'superbugs' – those very worrying bacteria that have become resistant to a large number, and in some cases, all available, antibiotics. Add to this the diminishing development of new antibiotics in the last 20 years and we could soon see a return to the Florence Nightingale era where infections caused more death than bullets because there were no effective drugs to treat these diseases. The introduction of tigecycline in the UK comes at absolutely the right time and will provide a vital new weapon in the fight against infection."

> "Difficult-to-treat, antibiotic-resistant and often life-threatening infections are a growing problem in the UK"

During development, Wyeth designed this drug to be capable of surmounting two common resistance mechanisms that develop in bacteria – the two key tetracycline-resistance mechanisms – efflux pumps and ribosomal protection. The drug is also unaffected by other bacterial mechanisms of resistance, such as extended-spectrum β-lactamases, which have limited the number of antibiotic options available to physicians.

In addition to the well-publicized infections with methicillin-resistant *Staphylococcus aureus* (MRSA), the drug will also be able to treat other important public health problems including infection with *Escherichia coli* and *Klebsiella*, for which there are currently very few available antibiotics.

Mark Palazzo, Chief of Service for Critical Care Medicine at Hammersmith Hospitals NHS Trust (London, UK) noted that "Until now, the lack of available antibiotic options for these more difficult-to-treat bacteria has necessitated the use of combination therapies – two or more different antibiotics – to fight the resistant bacteria". He continued that "Combination treatment can contribute to increased drug costs, drug interactions, with potentially higher patient risk and further increased antibiotic resistance, which complicates the treatment. It would be an advantage for patient care to have the option of a new single effective therapy".

To date, the most common reported side effects of the drug in clinical trials are nausea (29.5%) and vomiting (19.7%), which have generally been mild or moderate in severity. Tigecycline is supported by global *in vitro* studies and an *in vivo* clinical trials program.

Trastuzumab cardiac toxicity no cause for alarm

A group from the MD Anderson Cancer Center (TX, USA) have investigated the cardiac toxicity of trastuzumab (Herceptin®, Genentech Inc, Switzerland) and found that while the drug can cause heart problems, the effects are usually reversible. Owing to previous clinical trials of trastuzumab in combination with chemotherapy where approximately 10-26% of patients experienced cardiac toxicity, the drug is not recommended for patients with heart problems. The study published recently in the *Journal of Clinical Oncology* is the first to investigate the cardiac effects of trastuzumab outside of a clinical trial in patients who had been receiving the drug for at least 1 year. Patients are often administered with trastuzumab for several years, therefore the investigators felt that it was important to quantify any cardiac risks there might be.

Herceptin is a well-known drug and there has been some controversy surrounding its provision for patients in certain countries, such as the UK. The humanized monoclonal antibody is the standard of care for patients with human epidermal growth receptor (HER)2-positive breast cancer, who comprise approximately a fifth of breast cancer patients. Currently, it is Genentech's second-best selling drug, and in the first 6 months of 2006 sales were approximately CHF 1.81 billion.

Priority Paper Alerts

Atypical lymphoproliferation progressing into B-cell lymphoma in rheumatoid arthritis treated with different biological agents: clinical course and molecular characterization

Quartuccio L, De Re V, Fabris M. *Haematologica* 91, 691–694 (2006).

Describes a case of treatment of rheumatoid arthritis (RA) associated with a lymphoproliferative disorder (LPD) that developed after methotrexate and cyclosporin A therapy. Following antitumor necrosis factor-α therapy (for replapsing arthritis) an aggressive B-cell non-Hodgkin's lymphoma developed. The article highlights different safety profiles of a number of biological treatments in patients with RA and an associated B-cell nonmalignant LPD.

Outcome of treatment for congenital toxoplasmosis, 1981–2004: the National Collaborative Chicago-Based, Congenital Toxoplasmosis Study.

McLeod R, Boyer K, Karrison T *et al.* Toxoplasmosis Study Group. *Clin. Infect. Dis.* 42(10), 1383–1394 (2006).

Report of a long-term follow up of a group of 120 infants with congenital toxoplasmosis who were treated in the first year of life with the drugs pyrimethamine and sulfadiazine. Children were evaluated at birth and subsequent, predetermined intervals, to evaluate end points: motor abnormalities, cognitive outcome, vision impairment, formation of new eye lesions and hearing loss. Results showed generally favorable outcomes (although not for all children), which reiterate the importance of diagnosis and treatment of infants with the disease.

Effects of early treatment with statins on short-term clinical outcomes in acute coronary syndromes: a meta-analysis of randomized controlled trials.

Briel M, Schwartz GG, Thompson PL *et al*. *JAMA* 295(17), 2046–2056 (2006).

Evaluates the outcomes of patients in randomized, controlled trials on early statin therapy after the onset of acute coronary syndromes (ACSs) compared with placebo or the normal course of care over the short term (1 and 4 months) following ACS. It was determined that there is no reduction in death, myocardial infarction or stroke for up to 4 months, associated with the initiation of statin therapy within 14 days of the onset of ACS.

Gene therapy hope for cervical cancer

Scientists in Japan have been investigating the potential of using gene therapy for treating cervical cancer. K Hamada and colleagues from Ehime University (Japan) have been exploring the possibility of blocking the expression of human papilloma virus (HPV) oncogenes to treat HPV-positive cervical cancer. Owing to the fact that HPVs are identified in most cervical cancers, this study, published in the August issue of *Gynecologic Oncology*, brings promise for the treatment of cervical cancer.

The team of scientists introduced antisense RNA transcripts of the HPV type 16 genes, E6 and E7, via a recombinant adenoviral vector, into human cervical cancer cell lines that were harboring HPV 16. The E6 and E7 genes of HPVs encode proteins that interfere with the function of the tumor suppressor proteins p53 and retinoblastoma (Rb). Antisense RNA, a messenger (m)RNA transcript that is complementary to the endogenous mRNA, prevents HPV 16 E6 and E7 from being expressed.

They then analyzed the effects of expression of these genes on cell and tumor growth and found HPV 16 E6 and E7 antisense RNA was detected for 14 days in infected cervical cells. After infection, both E6 and E7 protein expression was suppressed and the expression of p53 and Rb increased.

Macroscopic effects of the treatment were also observed; the infected cervical cancer cell lines underwent apoptosis, both *in vitro* and *in vivo,* and tumors derived from them showed signs of suppressed cell growth and tumorigenicity.

Hamada concluded that this technique "might be a potentially useful approach to the therapy of HPV 16-positive cervical cancer."

Progress in the development of earlier detection systems for ovarian cancer

Research teams across the USA are currently exploring methods of earlier diagnosis of ovarian cancer. The techniques under investigation include biomarkers and nanotechnology.

Teams from the Roswell Park Cancer Institute and the University at Buffalo (NY, USA) have been conducting research into a simple blood test for early ovarian cancer detection. Using data from NMR imaging analyses of blood samples, analyzed using advanced computer modeling techniques, a biomolecular signature for early stage ovarian cancer has been recognized. Researchers hope that this could be developed into a screening test for ovarian cancer.

A different approach has been taken by researchers from Rush University Medical Center, in collaboration with Argonne National Laboratory and Illinois Institute of Technology, who hope that nanotechnology will proved new methods for diagnosis and treatment of ovarian cancer. Diagnosis of early stage cancer often involves the detection and characterization of very small amounts of biomarkers, it is hoped that a nano-based approach could help to resolve some of the issues faced.

Device to eradicate the pain of migraine before it begins

An electronic device known as transcranial magnetic stimulation (TMS) is set to become the next form of relief for the millions of people who suffer from debilitating migraine pain.

Initial studies to test the device, led by the Ohio State University Medical Center, USA neurology investigators, have demonstrated it to be effective in eliminating migraine pain when administered at the point of onset. A subsequent study will examine the device in a larger population.

The device acts by interrupting the aura phase of the migraine – the phase that precedes the headache. Migraine sufferers often describe 'seeing' showers of shooting stars, flashing lights and experiencing loss of vision, weakness, tingling or confusion. This is usually followed by a throbbing headache, nausea and vomiting.

Yousef Mohammad, the principal investigator of the study commented, "Perhaps the most significant effect of using the TMS device was on the 2-h symptom assessment, with 84% of the episodes in patients using the TMS occurring without noise sensitivity. Work functioning also improved, and there were no side effects reported."

A new device known as transcranial magnetic stimulation has been tested for the treatment of migraine by researchers in the USA and has so far shown positive results

The device sends a strong electric current through a metal coil, which creates an intense magnetic field for approximately 1 ms. This magnetic pulse, when held against a person's head, creates an electric current in the neurons of the brain, interrupting the aura before it results in a throbbing headache.

"The device's pulses are painless. The patients have felt a little pressure, but that's all", said Mohammad.

"In our study sample, 69% of the TMS-related headaches reported to have either no or mild pain at the 2-h post-treatment point compared with 48% of the placebo group. In addition, 42% of the TMS-treated patients graded their headache response, without symptoms, as very good or excellent compared with 26% for the placebo group. These are very encouraging results."

Up until the late 1990s it was believed that migraine headaches began with vascular constriction, which results in an aura, followed by vascular dilation, which leads to a throbbing headache. However, it was then discovered that neuronal electrical hyper-excitability resulted in a throbbing headache. This new understanding of the migraine mechanism was instrumental in the development of the TMS device.

Potential for new therapeutics against leukemia

A team of medical research fellows at the Howard Hughes Medical Institute (HHMI), Chevy Chase (MD, USA), have recently identified a novel mutation that is linked to the development of a cancer of the bone marrow - myelofibrosis with myeloid metaplasia (MF). The finding, published in the July 2006 issue of the *PLoS* journal, suggests a new target for therapeutic drugs used to combat such rare chronic leukemias, which are resistant to the leukemia drug, Gleevec®.

Yana Pikman, lead author of the PLoS Medicine article commented "Now we have two targets that may be useful in the search for drug treatments to control chronic leukemia. This new mutation is interesting because when we express it in mice, they get a very similar disease, so it may be a good model for testing drugs against leukemia".

A biological basis for obesity

New research has shown that weight gain in obese rats may be due to low activity levels, rather than excessive calorie consumption. The study was carried out as a joint effort by colleagues at the University of Minnesota, the Minnesota Obesity Centre and the Mayo Clinic, Rochester (MN, USA).

The researchers found that lean rats are more sensitive to the activity-stimulating chemical, orexin A. Minor physical activities induced by orexin A, such as fidgeting, and other movements associated with restlessness, help to control weight by burning calories.

"The greater expression of orexin receptors suggests the lean rats' brains were more sensitive to the orexin the brain produces" explains Catherine M. Kotz, senior researcher for the study, who went on to suggest that "the results point to a biological basis for being a couch potato"

Obesity-prone and obesity-resistant rats were developed by selective breeding and then used in a series of experiments in which different amounts of orexin A were given to the rats. Activity levels of individual rats were measured using sensors, revealing that the lean group moved significantly more than the obesity-prone group. Obesity itself was not responsible for reduced activity, as the experiments were carried out whilst the rats were young, all the same weight and on exactly the same diet.

Previous research has revealed that lean (human) individuals move around 2 h more a day than obese individuals. "Many people focus on diet (to control their weight), but it may be more feasible for some people to stand or move more throughout the day," comments Dr Kotz.

The full study appears in the *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*.