Notes from Singapore

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A new section of DrugScan where pharmacists and other health professionals from around the world offer insights and perspectives on medical issues from their own local perspective.

Docetaxel+carboplatin: active for NSCLC in Asian and Caucasian patients

Non-small cell lung cancer (NSCLC) is generally not chemosensitive. Despite the introduction of several new cytotoxic agents for advanced and metastatic NSCLC, there is no universally agreed standard drug combination for this disease. Cisplatin-containing regimens have shown a survival advantage. Docetaxel and carboplatin have shown activity against untreated advanced NSCLC in phase II trials. However, this has been predominantly reported in Caucasian patients. This combination has now been studied in a phase II trial of advanced (Stage IIIB, IV) NSCLC in Caucasian and Asian patients. A total of 66 patients (43 Caucasian, 23 Asian) were entered into the trial but only 62 were evaluable. The chemotherapy regimen comprised docetaxel 75mg/m² and carboplatin AUC 6 given every 3 weeks. Patients were aged 18 to 75 years, had the Eastern Cooperative Oncology Group performance status of 0 or 1, received no prior chemotherapy and no prior radiation was permitted for patients with stage IIIB disease. Patients with brain or leptomeningeal metastasis and those with symptomatic peripheral neuropathy (≥ grade 1) were excluded. The overall response rate was 42%; 65% Asian and 31% Caucasian patients (p = 0.01) responded. The one year survival rate was 53%. The median overall survival was 12.9 months. These results are comparable with other reports of this drug combination. Ethnicity was the only significant predictor of response in multivariate analysis. Performance status (p = 0.021), ethnicity (p = 0.035) and presence of bone or liver metastases (p = 0.011) were independent predictors of overall survival. Neutropenia (grade IV; 73%), febrile neutropenia (26%) and diarrhoea (grade III/IV; 11%) were major treatment-related toxicities. Asian patients from Singapore experienced a higher rate of febrile neutropenia requiring a reduction in the carboplatin dose to AUC 4.5. A previous study on the pharmacology of docetaxel in Asian patients showed that they have a slower plasma clearance than Caucasians, suggesting that this could be a main determinant of greater toxicity seen.

This study shows that docetaxel in combination with carboplatin is active in advanced NSCLC in Asian and Caucasian patients and the potential impact of ethnicity on efficacy and toxicity warrants further investigation.

(Willward MJ et al. Annals of Oncology 2003; 14: 449-54.)

Klebsiella pneumoniae an important community-acquired pathogen in adult CNS infections in East Asia

Klebsiella pneumoniae and other gram-negative bacilli are uncommon causes of CNS infections except among neurosurgical, hospitalised, and neonatal and paediatric patients. K. pneumoniae have rarely been reported in Europe and North America as a cause of community-acquired CNS infection. In contrast, Taiwan and Singapore have been reporting cases. A recent case series was reported by doctors in Singapore; all six patients (5 males, 1 female) were middle-aged and three were food handlers. K. pneumoniae was cultured from various sites: cerebrospinal fluid (CSF), aspirated abscess and blood. All isolates tested negative for extended spectrum beta-lactamase production and were sensitive to cephalothin, ceftriaxone, cefuzidime, amoxycillin + clavulanate, gentamin, amikacin, co-trimoxazole and ciprofloxacin. Five patients underwent craniotomies for drainage of the infections and one had a transsphenoidal repair for a CSF leak due to intracranial extension of sphenoid sinusitis. Antibiotics used included ceftazidime, cephalzin, ceftriaxone, metronidazole, cefotaxime and cloxacillin. Five of the six patients ultimately recovered and were discharged without long-lasting neurological sequelae. One patient relapsed with a K. pneumoniae scalp abscess four months later, and ultimately recovered. Occupational exposure is suggested as a possible risk factor. The current case series with three food handlers raises the possibility of food-borne route of infection. K. pneumoniae remains an important cause of community-acquired CNS infection in adults and should be increasingly recognised as a cause of such infections in East Asia.

(Habib AG et al. Eur J Clin Microbiol Infect Dis 2003; 22: 486-8.)

ARDS in critically ill SARS patients

Severe acute respiratory syndrome (SARS) first emerged in November 2002, was initially described in March 2003 and is thought to be caused by a novel coronavirus. About 25% of patients with SARS are likely to progress to respiratory failure. Mortality is high. In Hong Kong, the mortality rate was 13.2% for patients younger than 60 years and 43% for those aged 60 years or over. A recent case series from Singapore reported 28 day mortality of 10.1% of 199 patients and 37% of 46 patients in the intensive care unit (ICU). ICU mortality at 13 weeks was 52.2%. ICU survivors (n = 22) were divided into three subgroups based on clinical course: early recovery without mechanical ventilation, intermediate recovery with mechanical ventilation for 14 days or less, and late survival with mechanical ventilation for more than 14 days. The groups differed in age, APACHE II score, baseline P/F/FiO₂ ratio, and peak lactate dehydrogenase levels. The early recovery group had a short acute lung injury, those in the intermediate recovery group had improvement in oxygenation and pulmonary compliance.

Breaking News

(For full references refer to the Journal page on the SHPA web site <www.shpa.org.au>)
Late survivors had a protracted and severe course of acute respiratory distress syndrome (ARDS) and complications. APACHE II score, P/F0/FiO2 ratio were predictors of early/intermediate recovery. The odds ratio of recovery was inversely proportional to APACHE II score whilst P/F0/FiO2 ratio was directly proportional. As for drug treatment, 16 eligible ICU probable SARS patients with acute lung injury or ARDS, but without any bacterial or fungal infection were given intravenous pulsed methylprednisolone (200 mg) and high dose intravenous immunoglobulin (0.4g/kg body weight) once daily for three days as an immunotherapy regimen. These findings provide useful information for optimising supportive care for SARS-related critical illness. (Lew TW et al. JAMA 2003; 290: 374-80.)

ONCOLOGY
Michael Cain

Bortezomib looks good for myeloma and probably more
Move over Glivec? Racing to prominence in record time is bortezomib. Known previously as PS-341, and now marketed in the USA as Velcade, bortezomib is a reversible proteasome inhibitor—the first of its class. Proteasomes are essentially a rubbish removal system: they disassemble a broad range of signal transduction proteins critical to apoptosis, angiogenesis, and cell cycle regulation. Proteasome blockade disables cancer survival pathways and increases cancer cell chemosensitivity. Bortezomib will likely prove useful against multiple cancers but it is its anti-myeloma activity that has propelled it forward. In the first fully reported phase II study, one-third of 202 heavily pre-treated patients (median six prior therapies) given bortezomib experienced a substantial response. In seven cases, no evidence of myeloma remained, and in twelve cases, disease was only demonstrable with the aid of immunofixation. Overall median survival was sixteen months; median response duration was twelve months. Major side effects were fatigue, thrombocytopenia, peripheral neuropathy, and neutropenia. Serious (grade IV) toxicity affected 14% of cases. Longer term studies and trials involving other malignancies are in progress. (Richardson PG et al. N Engl J Med 2003; 348: 2609-17.)

Rigorous assessment suggests promise with anti-emetic aprepitant
The introduction of ondansetron a decade ago expanded the understanding of cytotoxic-induced nausea and vomiting (CINV), raised expectations about control, and facilitated greater migration of chemotherapy to outpatient administration. CINV has been substantially tamed but still exists for many, and is problematic for a few. Most CINV studies have counted vomits and time with nausea. These are de facto indicators of impact on patient functioning and quality of life, but a better measure that is obtained directly was used in a recent assessment of a new class of antiemetics, the neurokinin-1 (NK-1) receptor antagonists. The functional living index—emesis (FLIE) is a tool that quantifies how much CINV affects a patient’s ability to function, enjoy normal living, and to relate with friends and family. In a study of nearly 400 cisplatin-treated patients the effectiveness of adding aprepitant (the first NK-1 antagonist approved by the FDA) to a combination of ondansetron and dexamethasone was tested using FLIE. Over the assessment period of five days, the percentage of patients functionally unaffected by CINV rose from 66 to 84%. Should there be widespread adoption of aprepitant? No, not yet. Substantial drug interaction issues exist and the ultimate benefit in other non-cisplatin settings need to be assessed. (Martin AR et al. Eur J Cancer. 2003; 39: 1395-401.)

Even small details can change the effects of chemotherapy
The devil is in the detail! Delivering a cytotoxic chemotherapy protocol can be a complex business. Many points of detail, known and yet to be known, can alter treatment efficacy and/or toxicity. Rate and sequence of administration may be important, as may be the selection of supportive care drugs, avoidance of unrelated drug interactions and monitoring specifications. Often detailed guidance is not available in original literature reports. The potential relevance of small details is illustrated in a recent study examining the effect of varied sodium content of hydration fluid used in conjunction with high-dose methotrexate. A group of 30 children with acute lymphocytic leukaemia who were to be treated with high-dose methotrexate received hydration with a sodium content of 70 mEq/L or 100 mEq/L in a randomised cross over design. Plasma methotrexate levels at 24 hours were less with the higher sodium load but not significantly so. At 48 hours the difference was more than 50% (p = 0.04) and at 72 hours there was almost a three fold difference (p = 0.003). In this cohort adverse events remained similar for the two regimens, but in other settings variance of this magnitude could be clinically relevant. (Kinoshita A et al. Cancer Chemother Pharmacol 2003; 51: 256-60.)

GASTROENTEROLOGY
Dave Cosh

Acid suppression not linked to malignancy
Concerns that gastric acid suppression with cimetidine may increase the risk of death from malignancy of the gastrointestinal tract led Colin-Jones and others to demonstrate that this was not the case. They achieved this by comparing observed deaths (cause and rate) amongst users and non-users of cimetidine in the UK. The same group has now employed the same methodology to seek an answer to the same question, substituting omeprazole for cimetidine. They reviewed 17,936 users of omeprazole over four years. In the group of omeprazole users, death rates from any malignancy were higher at year one (observed 217 versus expected 119) and the same trend was seen with circulatory and respiratory disorders and nonmalignant digestive disease. These differences were no longer apparent at year four. The fact that oesophageal cancer and liver disease were seen more commonly in the omeprazole group across the whole four-year follow-up period is not thought to be an indication of drug-induced disease, but rather a reflection of the presence of a disorder for which the drug was prescribed. A note of caution: longer follow-up will be needed to provide greater comfort. (Bateman DN et al. Gut 2003; 52: 942-6.)
Losartan to reduce portal pressure?

Thirty-nine patients with biopsy-proven cirrhosis of the liver were randomised to receive either propranolol 40 mg twice daily or losartan 25 mg daily, to evaluate the comparative efficacy of the two agents in reducing portal pressure. At baseline and on day 14, hepatic venous pressure gradients were measured (it is known that a hepatic venous pressure gradient reduction of 20% over baseline significantly reduces the risk of oesophageal varicose bleeds). Those achieving this level of pressure reduction were designated as ‘responders’. Seventy-nine per cent (15/19) of those taking losartan responded compared with 45% (9/20) treated with propranolol. The response to losartan was achieved without a change in blood pressure or pulse rate. The dose of propranolol was titrated to a 25% reduction in pulse rate (compared with baseline) providing that it did not drop below 55 beats per minute. The difference in favour of losartan was seen in a subset of the group defined as alcohol abusers. It is important to note that the endpoint of the study was a reduction in portal pressure (not actual bleeding), but that the favourable relationship between reduced bleeding risk and portal pressure reduction is well established.

(De BK et al. Am J Gastroenterol 2003; 98: 1371-6.)

Pulse cyclophosphamide for inflammatory bowel disease

Seven patients with an acute exacerbation of steroid-refractory inflammatory bowel disease (IBD)—defined as treatment failure after seven days of prednisolone (at least 50 mg per day)—were given intravenous pulsed cyclophosphamide (750 mg). Mesna was administered to protect the bladder and further doses of cyclophosphamide were given at monthly intervals, during which time an attempt was made to wean patients down to the lowest possible dose of oral prednisolone. Azathioprine 2.5mg/kg/day was given as a maintenance drug after the onset of remission. Six patients achieved remission that was maintained for a median period of 18 months, and two of these enjoyed a significant reduction in maintenance steroid dose. Side effects were minimal (two cases of candida oesophagitis). Pulse treatment with cyclophosphamide has proven efficacy in other inflammatory disorders (e.g. systemic vasculitis) but experience in IBD is limited. Severe flares of IBD carry the risk of surgical resection—a prospect feared by patients. Medical therapy that can reduce the need for surgical intervention will always be attractive and the results of this small series are encouraging.

(Stallmach A et al. Gut 2003; 52: 377-82.)

PHARMACY PRACTICE

Rosemary Burke

Teaching medication management skills

Pharmacist-facilitated teaching sessions in skills relevant to medicines management has proven to be beneficial for pre-interns in a study recently conducted in the UK. Five practical sessions (20 minutes each) for twenty students were provided using a workstation approach. Topics covered included managing anticoagulation, preparing intravenous medication, taking a patient history and writing an inpatient prescription, writing a discharge prescription (including a narcotic) and inhaler technique: none of these topics had been taught in medical school. The effectiveness was tested one month later by a practical demonstration and an assessment of confidence in performing the task. This assessment exercise utilised two control stations (calculations, and the use of the British National Formulary) and a control group of pre-interns who had not received the teaching sessions was also studied. There was no difference in the performance or confidence of the active and control groups in the inhaler session, but the active group reported more confidence in the anticoagulation and discharge exercises: these skills probably needed more sessions to achieve increased competence. The remainder of the exercises revealed an improvement in both performance and confidence for the active group, but the control station involving calculations caused problems for both groups. Some skills interns must use from the outset of their work are not taught in medical schools. Many hospital pharmacists are involved in orientation programs for interns and programs for pre-interns, and these are often didactic rather then experiential. This research underscores the importance of learning these skills, and hospital pharmacists are ideally positioned to do the teaching.

(Scobie SD et al. Med Educ 2003; 37: 434-7.)

Intravenous drug errors examined

An observational study of patients receiving IV drugs in two British hospitals found errors (defined as a deviation in preparation or administration of a drug from a doctor’s prescription, the hospital’s or manufacturer’s protocol which could adversely affect the patient) occurred in 49% of 430 episodes observed. There were three severe errors, 126 moderate errors and 83 potentially minor errors. The more severe errors occurred at the preparation stage, with multiple-step preparations such as using the incorrect solvent or preparing an incorrect dose being implicated. The more severe errors included a rapid bolus of vancomycin, and the incorrect vial of heparin being selected (resulting in a fivefold overdose). The majority of the errors (73%) involved the administration of the drug too quickly. The investigators concluded that errors could be reduced by decreasing the amount of preparation required on the ward, provision of training, and by introducing technology to administer slow bolus doses of drugs. Pharmacists need to be aware of potential problems with intravenous administration when assisting with the development of policies for drug use. Most incident-based reporting systems rarely detect these problems. Multiple-step preparations could be considered for centralised preparation, and technology could in the future help reduce the potential to give bolus doses too quickly. The Institute of Safe medication practice recently has published a list of drugs where giving a medication too quickly can cause problems (www.ismp.org/MSArticles/hw.htm).

(Taxis K et al. BMJ 2003; 326: 684-7.)

Computer simulation as a basis for pharmacy re-engineering

In 1992 the Emory University hospital pharmacy in Atlanta concluded that their current facility design was inappropriate to support future requirements. Their system had distribution services managed remotely from four pharmacy satellites with support from a central pharmacy. All services except total parenteral nutrition, purchasing and inventory control were provided from the satellites. A consultant was hired to help with the re-engineering of the service and was to use computer
simulation to compare centralised and decentralised models for the distribution of sterile and unit dose packages. Four scenarios were developed involving combinations of centralised sterile products and unit dose systems using pyxis profiles or robotics. Data regarding workflow and layout design were collected. Computer simulations defined the number of staff required for each option. The simulation resulted in a recommendation for centralisation of sterile production, and either of the automated options (depending on whether reduction in staff or cost was the driving factor). Although pharmacy and nursing staff had some doubts with some of the conclusions from the simulation, the decision was to centralise unit dose dispensing using robotics and to close three of the four satellite pharmacies. After the process was implemented there had been a reduction in staff numbers to a greater extent than had been predicted, but the change in operational costs (when benchmarked with other institutions) had not been realised and some predicted outcomes with respect to turnaround times had not occurred. This experience demonstrates some of the advantages and disadvantages with using computer simulation to determine a business case for a proposed change involving automation. In Australia many hospitals are looking at automation options and care needs to be taken when analysing the benefits outlined from other sources. Managers and staff must be involved in the review, planning and implementation of any proposed restructuring or change, as systems change does not always reliably produce the expected benefits. (Buchanan EC. Nurs Adm Q 2003; 27: 33-40.)

RESPIRATORY MEDICINE
Karim Nyfort-Hansen

Inhaled corticosteroid doses in asthma
In 2001, Drugscan reviewed a meta-analysis investigating the dose-response relationship of inhaled fluticasone in asthma, which concluded that most of the therapeutic effect of inhaled fluticasone is achieved with a total daily dose of 100-250 micrograms. Despite this evidence high doses of inhaled corticosteroids (ICS) continue to be widely prescribed. A recent evidence-based analysis of the efficacy and safety of different doses of ICS for asthma has summarised the results in terms of the number needed to treat (NNT) and number needed to harm (NNH). Data was extracted from six systematic reviews on the Cochrane Database, but a relatively small number of trials with budesonide and beclomethasone meant that only the dose-response effects of fluticasone could be evaluated. The results confirm that ICS are highly efficacious, with NNT to prevent one person developing a significant deterioration in asthma control of 2.1 (1000 µg daily), 2.0 (500 µg daily) and 2.9 (100 µg daily). The NNH for clinically significant hoarseness/dysphonia was 152 (100 µg daily), 23 (500 µg daily) and 17 (1000 µg daily). Similarly the NNH for oral candidiasis was 90 (100 µg daily), 21 (500 µg daily) and 6 (2000 µg daily). The authors conclude that Level 1 evidence supports the use of low-dose ICS in asthma, with an increase in side-effects being the main effect of increasing ICS dose. (Powell H et al. Med J Aust 2003; 178: 223-5.)

Inhaled steroids in asthma – is less better?
Further support for the use of lower doses of ICS in asthma comes from a Scottish primary care trial, in which 259 patients with chronic stable asthma were randomised to continue their usual high dose of ICS (fluticasone or beclomethasone, mean dose of beclomethasone dipropionate (BDP) or fluticasone equivalent 1430 µg daily) or receive a 50% reduction in dose if they met criteria for stable asthma. Patients were followed up at three monthly intervals for one year, with the main outcome measures being exacerbation rates, asthma-related visits to general practice and hospital, health status and corticosteroid dosage. On average the stepdown group received 25% less ICS than the controls (1067 µg versus 1415 µg BDP daily) with no significant difference in any of the main outcome measures. Forty patients (31%) in the stepdown group and 33 (26%) of the control group experienced at least one asthma exacerbation over the one year study period (OR 1.29; 95% CI 0.75-2.23; p = 0.354). This is the first randomised controlled trial to investigate the longer term clinical implications of stepping down ICS dosage in patients with moderate to severe asthma, and the results provide valuable evidence in support of the stepdown approach to ICS dosage advocated in asthma management guidelines. (Hawkins G et al. BMJ 2003; 326: 1115.)

Canadian SARS cases analysed
The outbreak of severe acute respiratory syndrome (SARS) earlier this year is likely to remain the most widely publicised medical news story of 2003. Initial reports described the clinical features of small numbers of patients, and were followed by larger retrospective case series. In one of these, Canadian clinicians have described the clinical features, treatment and short-term outcomes of 144 patients with SARS in the greater Toronto area. Most patients (95%) received empirical antibiotic therapy as per the Canadian guidelines for the management of community-acquired pneumonia. Ribavirin was used for 88% and steroids for 40% of patients. Most patients who received ribavirin were administered a loading dose of 2000 mg intravenously, followed by 1000 mg IV every six hours for four days, followed by 500 mg every eight hours for three days. The mean treatment course was six days. Ribavirin was associated with significant toxicity, including haemolysis (76%), a decrease in haemoglobin > 2 g/L (49%) and elevation of transaminases (40%). These toxicities led to the premature discontinuation of ribavirin in 18% of patients. Twenty-nine patients (20%) were admitted to the intensive care unit, and eight patients died (6.5% mortality rate at 21 days). Although poor outcomes were more common for those treated with ribavirin, this was not statistically significant (RR 1.9; 95% CI 0.45-8.0; p = 0.36). (Booth CM et al. JAMA 2003; 289: 2801-09.)

NEUROPSYCHIATRY
Chris Alderman

Aripiprazole provides yet another antipsychotic option
The latest arrival on the international landscape of antipsychotic drug options is aripiprazole, an agent with a relatively novel mechanism of action distinguished by its effects as a partial agonist at dopamine D2
receptors. Now available in Australia and worldwide, this drug was the subject of a recent pooled analysis of safety and tolerability data from five short-term (4 to 6 week) trials. Although the duration of the studies used for this analysis was arguably insufficient to provide data that can be regarded with total confidence, the results appear to point towards acute adverse event rates similar to placebo, and lower rates of akathisia, extrapyramidal side effects and sedation than those seen with the comparator drug haloperidol. No deaths were reported in any of the studies, and the rate for serious adverse events was approximately 2.5% with both haloperidol and aripiprazole and 3.2% with placebo (mostly accounted for by psychosis). The studies were probably too short to allow any meaningful interpretation of the incidence of weight gain, but reassuringly, there was no indication that aripiprazole was associated with prolongation of the QTc interval. (Marder SR et al. Schizophr Res 2003; 61: 123-36.)

Relative toxicity of various antidepressants in overdose
That some of the newer generation antidepressants, specifically the Selective Serotonin Reuptake Inhibitors (SSRIs) are less toxic in overdose than their antecedents such as the Tricyclic Antidepressants (TCAs) is hardly startling news for practitioners with an interest in psychiatry or toxicology. Of more significance, however, are the results of a recent study that suggest that another new generation antidepressant, venlafaxine, may carry greater risk in the context of overdose than the SSRIs. Whyte et al studied 538 first-time admissions to hospital with deliberate self-poisoning with antidepressants, and found that 14% of patients with a venlafaxine overdose had seizures (in each case the dose was greater than 900 mg). Seizures were more likely with venlafaxine than with TCAs (OR 4.4; 95% CI 1.4–13.8). Along with SSRIs, venlafaxine was more likely to cause serotonin toxicity but less likely to cause coma than the TCAs. Although no patients in the cohort died, the likelihood of intensive care unit admission was less with the SSRIs than with other drugs, in keeping with the observation that these drugs were less likely to broaden the QRS complex to > 100 ms than was venlafaxine. We are left to ponder the wisdom of choosing venlafaxine as an antidepressant option for patients with significant risk for suicide by overdose. (Whyte IM et al. QJM 2003; 96: 369-74.)

First long-acting atypical antipsychotic sees market
Researchers have recently published the results of short-term study that has assessed the efficacy and safety of the first long-acting atypical antipsychotic (long-acting injectable risperidone) for patients with schizophrenia. The study extended over twelve weeks and involved the fortnightly intramuscular injection of a placebo or a dose of long-acting risperidone at a dose of 25 mg, 50 mg, or 75 mg. The total score on the Positive and Negative Syndrome Scale (PANSS) was decreased from baseline in each of the groups receiving the active drug, whereas the score increased in the group receiving placebo. Extrapyramidal symptoms were reported by 13% of patients receiving placebo and 10% of patients receiving 25 mg risperidone fortnightly, but these effects were more pronounced at higher doses. The arrival of a long-acting formulation of an atypical antipsychotic is indeed a welcome addition to the range of treatment options available for the management of schizophrenia. Funders will now need to decide whether the inevitable expense associated with the advent of new pharmaceutical product technology is acceptable when compared to the costs associated with standard oral maintenance therapy with atypical antipsychotics.
(Kane JM et al. Am J Psychiatry 2003; 160: 1125-32.)

INFECTIOUS DISEASES

Jeff Hughes

Oseltamivir brings added benefits for influenza
Oseltamivir is effective in reducing influenza-related Lower Respiratory Tract Complications (LRTCs), associated antibiotic use and hospitalisation. Analysis of data from ten placebo-controlled, double blind studies involving 3564 subjects (age range: 13 to 97 years) found oseltamivir reduced the use of antibiotics for any reason by 26.7%, the incidence of LRTCs by 55% and the episodes of hospitalisation by 59% amongst patients with confirmed influenza. In contrast, antibiotic use, LRTCs and hospitalisations were similar amongst oseltamivir and placebo recipients with influenza-like illness but for whom influenza was not confirmed. The benefits of oseltamivir were evident amongst healthy and ‘at-risk’ adults. (Kaiser L et al. Arch Intern Med 2003; 163: 1667-72.)

Outcomes mixed with tifacogin
Administration of tifacogin, a tissue factor pathway inhibitor, has no effect on all-cause mortality in patients with severe sepsis and a high International Normalised Ratio (INR). Further, administration of this drug is associated with an increased risk of bleeding, irrespective of the baseline INR. In a recent study 1754 patients (age ≥ 18 years) were randomised to receive either tifacogin (0.025mg/kg/hour for 96 hours) or placebo. For patients with sepsis and an elevated INR (≥ 1.2) who received tifacogin, the overall mortality after 28 days was 34.2% compared with 33.9% in the placebo group. However, overall mortality was lower amongst those patients whose initial INR was low (< 1.2) when given tifacogin, compared to those given placebo (12% versus 22.9%). Bleeding complications were significantly increased with the administration of tifacogin irrespective of the initial INR (high INR: tifacogin 6.5% versus placebo 4.8%; low INR: 6.0% versus 3.3%). (Abraham E et al. JAMA 2003; 290: 238-47.)

Azithromycin may outperform clarithromycin for pneumonia
Spanish investigators report that the combination of azithromycin plus ceftriaxone may offer benefits over the combination of clarithromycin plus ceftriaxone for patients with community-acquired pneumonia. In a cohort of patients who were matched on the basis of disease severity scores (as defined by the Pneumonia Patient Outcomes Research Team study group), patients receiving a three-day course of azithromycin (n = 383) compared to a ten-day course of clarithromycin (n = 220) had a significantly shorter length of hospital stay (7.4 +/- 5 days versus 9.4 +/- 7 days; p < 0.01) and lower mortality rate (3.6% versus 7.2%; p < 0.05). (Sanchez F et al. Clin Infect Dis 2003; 36: 1239-45.)
Melatonin and quality of sleep in the elderly
A bedtime dose of 5 mg melatonin for healthy volunteers over the age of 65 years did not provide any objective benefit in sleep quality or sleep latency amongst problem sleepers who were evaluated in a recent study. Subjects were screened using the mini-mental state examination (MMSE), the Geriatric Depression Scale (GDS) and Pittsburg Sleep Quality Index (PSQI). They were classified as normal or problem sleepers and randomly allocated to treatment or placebo in a crossover study of four-week blocks (including a washout period). Sleep diaries and remote sensor monitors attached to the non-dependent arm recorded motor activity and were used to assess sleep latency, sleep duration, number of awakenings and sleep efficacy. Treatment effects were calculated for each participant as the difference between the means of treatment and placebo. Very few side effects were reported and the mean 24-hour urinary metabolite of melatonin was not significantly different between the two groups. On the seven measures of sleep performance there was no significant difference between the sleep characteristics on melatonin or placebo for either the problem sleepers or the normal group. For high and low melatonin secretors there was no significant difference in efficacy.
(Basket JJ et al. Age Ageing 2003; 32: 164-70.)

Alzheimer's disease and chronic anticholinergic exposure
In a group of patients with Alzheimer's disease and treated with donepezil, the concomitant use of one or more other drugs with anticholinergic activity was associated with an increased loss of cognitive function. All subjects were treated with donepezil at a dose at least 10 mg per day and the doses of drugs with anticholinergic activity were not changed over the two-year period of the study. Assessments of cognitive function were undertaken using the mini-mental state examination (MMSE), and it is suggested that the natural history of Alzheimer's disease results in a loss of 3.5 points per year on the MMSE. Those receiving donepezil without any co-prescribed drugs with anticholinergic activity had a mean loss of 3.08 points in MMSE over two years. Although after one year there was no significant difference in the decrease in MMSE score between the two groups, at the end of two years those exposed to chronic anticholinergic activity had a mean decrease in MMSE scores of seven points. Because of the small number of subjects it was not possible to establish the relationship between the number of anticholinergic drugs and the decline in MMSE scores.
(Lu CJ et al. Am J Geriatr Psychiatry 2003; 11: 458-61.)

NSAID use and Alzheimer's risk
The risk of developing Alzheimer's disease appears to be lowered by the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and the level of protection seems to be greater the longer these agents are used. Three separate sets of data analysis for the meta-analysis of observational studies have focused upon Alzheimer's disease and the use of all NSAIDs, the incidence of Alzheimer's disease and the use of aspirin, and the duration of NSAIDs use in these studies. Because there was a lack of definitive data in the studies on the outcome for vascular dementia, this clinical entity was not analysed separately. The pooled relative risk of developing Alzheimer's disease from the nine studies was 0.84 (0.54–1.05) in the cohort studies, 0.62 (0.45–0.82) among the case-control studies and 0.72 (0.56–0.94) in both. This later score represents a risk reduction of 30% for the development of Alzheimer's disease. The pooled relative risk from the eight studies of aspirin users was 0.87 (0.70–1.07) and only a modest reduction in risk of 13%. The risk was 0.95 (0.70–1.29) for less than one months use, 0.83 (0.65–1.06) for less than 24 months and 0.27 (0.13–0.58) for greater than 24 months use.
(Etminan M et al. BMJ 2003; 327:128-33.)