# table of contents

## WORLD REPORT

### France's president faces backlash over healthcare reforms
Ionescu, C.

### The global fund: 5 years on
McCarthy, M

### Abortion debate heats up in Latin America
Repogle, J.

### US Congress eyes CDC’s lingering morale problems
Young, A.

## ARTICLES

### Recurrence rates of video-assisted thoracoscopic versus open surgery in the prevention of recurrent pneumothoraces: a systematic review of randomised and non-randomised trials
Barker, A., Eleni C Maratos, Lyn Edmonds, and Eric Lim.

### Assessment of fludarabine plus cyclophosphamide for patients with chronic lymphocytic leukaemia (the LRF CLL4 Trial): a randomised controlled trial
Catovsky, D., S Richards DPhil, E Matutes, D Oscier, MJS Dyer, RF Bezares, AR Pettitt, T Hamblin, and DW Milligan.

### Exposure to substances in the workplace and new-onset asthma: an international prospective population-based study (ECRHS-II)

### Efficacy and safety of combined use of aliskiren and valsartan in patients with hypertension: a randomised, double-blind trial.
Oparil, S., Steven A Yarows, Samir Patel, Hui Fang, Jack Zhang, and Andrew Satlin.

### Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review.
Moore, T.H.M., Stanley Zammit, Anne Lingford-Hughes, Thomas RE Barnes, Peter B Jones, and Glyn Lewis.

### Diaphragm and lubricant gel for prevention of HIV acquisition in southern African women: a randomised controlled trial.
Padian, N.S., Ariane van der Straten, Gita Ramjee, Tsungai Chipato, Guy de Bruyn, Kelly Blanchard, Stephen Shiboski, Elizabeth T Montgomery, Heidi Fancher, Helen Cheng, Michael Rosenblum, Mark van der Laan, Nicholas Jewell, and James McIntyre.

### A treatment protocol for infants younger than 1 year with acute lymphoblastic leukaemia (Interfant-99): an observational study and a multicentre randomised trial
Pieters, R., Martin Schrappe, Paola De Lorenzo, Ian Hann, Giulio De Rossi, Liisa Hovi, Thierry LeBlanc, Tomasz Szczepanski, Alice Ferster, Gritta Janka, Jeffrey Rubnitz, Lewis Silverman, Jan Stary, Myriam Campbell, Chi-Kong Li, Georg Mann, Ram Suppiah, Ajay Vora, and Maria Grazia Valsecchi.

## SERIES: Psoriasis

### Pathogenesis and clinical features of psoriasis
Griffiths, C.E.M., and Jonathan NWN Barker.

### Current and future management of psoriasis
Menter, A., and Christopher EM Griffiths.

## SEMINAR

### Chronic myeloid leukaemia
Hehlmann, R., Andreas Hochhaus, and Michele Baccarani.

## REVIEW

### Outcome of assisted reproduction

France’s President, Nicolas Sarkozy, is planning to introduce a new tax for anyone seeking state medical assistance in France. But he faces opposition from doctors who have branded the reform socially unjust and dangerous to public health. Carmiola Ionescu reports from Paris. With an outstanding health-care deficit of nearly €6 billion at the end of 2006 but with a health-care system declared the most consumer friendly in the European Union, France is facing a paradox. Patients, academics, and other senior medical staff in the health service are happy with the way things are going, but other medical staff and the debt-burdened new administration say it is high time that reforms are implemented.


The Global Fund to Fight AIDS, Tuberculosis and Malaria has become a major force in global health in just 5 years. In April, a new executive director took the helm of the organisation. Will he need to change the way it operates to fulfil its growing role? Michael McCarthy reports. This spring the Global Fund to Fight AIDS, Tuberculosis and Malaria announced that its programmes had treated nearly 3 million tuberculosis patients, distributed more than 30 million insecticide-treated bednets, and were providing antiretroviral drugs to more than 1 million people infected with HIV. After nearly 5 years of operation “Global Fund programmes are saving 3000 lives a day”, says the Fund’s new executive director Michel Kazatchkine.


The debate over abortion is resurgent in largely Roman Catholic Latin America. Some of the most religious jurisdictions in the region are loosening restrictions on the procedure while other countries, such as Nicaragua, are firmly clamping down. Jill Replogle reviews the situation. Both pro-choice and anti-abortion activists have been busy in Latin America during the past few years amid big legal changes in several countries. After Colombia loosened its previously strict anti-abortion legislation in May, 2006, Nicaragua passed one of the strictest anti-abortion laws in the region, in November of the same year. Then, Mexico City swung in the other direction by legalising abortion in April this year. The abortion debate . . .


An ambitious effort to reorganise the US Centers for Disease Control and Prevention has triggered morale problems at the agency, an exodus of senior staff—including high-profile scientists—and, now, investigations by the US Congress. Alison Young reports from Atlanta. Over the past 3 years, the US Centers for Disease Control and Prevention (CDC) has been roiled by internal turmoil and an exodus of high-profile scientists. Now questions about the agency’s leadership are drawing increased scrutiny from members of Congress. Their concern is that a massive reorganisation of one of the world’s premier public-health institutions, strategic changes in its focus, and the loss of key staff may be harming its scientific ability. In its storied 60-year history, the CDC finds itself in an unusual and uncomfortable position.

ARTICLES


Evidence supporting similar recurrence rates between video-assisted and open surgery for the treatment of recurrent pneumothorax is questionable, because the number of randomised trials is sparse and they are underpowered to detect any meaningful difference. Our aim was to do a systematic review of randomised and non-randomised studies to compare recurrence rates between the two forms of surgical access. We did a systematic literature search for studies on pneumothorax surgery in Medline, Embase, Cochrane Library, trial registers on the internet, and conference abstracts, and identified 29 studies (four randomised and 25 non-randomised) eligible for inclusion. Meta-analysis was done by combining the results of reported recurrence rates in patients undergoing video-assisted thoracoscopic surgery compared with those having open surgery. Both fixed and random effects models were applied to the results pooled for analysis. In studies that did the same pleurodesis through two different forms of access, the relative risk (RR) of recurrences in patients undergoing video-assisted surgery compared with open surgery was similar between non-randomised and randomised studies (RR 4·880 [95% CI 2·670–8.922] vs 3·951 [0·858–18·193]), yielding an overall RR of 4·731 (2·699–8.291; p<0·0001). There was no evidence to suggest heterogeneity of trial results (p=0·88). The high RR of recurrence for video-assisted surgery remained
robust to a random effects model (4·051 [1·996–7·465]; p<0·0001), by including all comparative studies (3·991 [2·584–6·164]; p<0·0001), with only high-quality studies used (4·016 [1·8468–7·736]; p<0·0001), and on a simulation biased in favour of video-assisted surgery when there were no events in either group (3·559 [2·165–5·852]; p<0·0001). Both randomised and non-randomised trials are consistent in recurrence of pneumothoraces and show a four-fold increase when a similar pleurodesis procedure is done with a video-assisted approach compared with an open approach.


Previous studies of patients with chronic lymphocytic leukaemia reported high response rates to fludarabine combined with cyclophosphamide. We aimed to establish whether this treatment combination provided greater survival benefit than did chlorambucil or fludarabine. 777 patients with chronic lymphocytic leukaemia requiring treatment were randomly assigned to fludarabine (n=194) or fludarabine plus cyclophosphamide (196) for six courses, or chlorambucil (387) for 12 courses. The primary endpoint was overall survival, with secondary endpoints of response rates, progression-free survival, toxic effects, and quality of life. Analysis was by intention to treat. There was no significant difference in overall survival between patients given fludarabine plus cyclophosphamide, fludarabine, or chlorambucil. Complete and overall response rates were better with fludarabine plus cyclophosphamide than with fludarabine (complete response rate 38% vs 15%, respectively; overall response rate 94% vs 80%, respectively; p<0·0001 for both comparisons), which were in turn better than with chlorambucil (complete response rate 7%, overall response rate 72%; p=0·006 and 0·04, respectively). Progression-free survival at 5 years was significantly better with fludarabine plus cyclophosphamide (36%) than with fludarabine (10%) or chlorambucil (10%; p<0·00005). Fludarabine plus cyclophosphamide was the best combination for all ages, including patients older than 70 years, and in prognostic groups defined by immunoglobulin heavy chain gene (VH) mutation status and cytogenetics, which were tested in 533 and 579 cases, respectively. Patients had more neutropenia and days in hospital with fludarabine plus cyclophosphamide, or fludarabine, than with chlorambucil. There was less haemolytic anaemia with fludarabine plus cyclophosphamide (5%) than with fludarabine (11%) or chlorambucil (12%). Quality of life was better for responders, but preliminary analyses showed no significant difference between treatments. A meta-analysis of these data and those of two published phase III trials showed a consistent benefit for the fludarabine plus cyclophosphamide regimen in terms of progression-free survival. Fludarabine plus cyclophosphamide should now become the standard treatment for chronic lymphocytic leukaemia and the basis for new protocols that incorporate monoclonal antibodies.


The role of exposure to substances in the workplace in new-onset asthma is not well characterised in population-based studies. We therefore aimed to estimate the relative and attributable risks of new-onset asthma in relation to occupations, work-related exposures, and inhalation accidents. We studied prospectively 6837 participants from 13 countries who previously took part in the European Community Respiratory Health Survey (1990–95) and did not report respiratory symptoms or a history of asthma at the time of the first study. Asthma was assessed by methacholine challenge test and by questionnaire data on asthma symptoms. Exposures were defined by high-risk occupations, an asthma-specific job exposure matrix with additional expert judgment, and through self-report of acute inhalation events. Relative risks for new onset asthma were calculated with log-binomial models adjusted for age, sex, smoking, and study centre. A significant excess asthma risk was seen after exposure to substances known to cause occupational asthma (Relative risk=1·6, 95% CI 1·1–2·3, p=0·017). Risks were highest for asthma defined by bronchial hyper-reactivity in addition to symptoms (2·4, 1·3–4·6, p=0·008). Of common occupations, a significant excess risk of asthma was seen for nursing (2·2, 1·3–4·0, p=0·007). Asthma risk was also increased in participants who reported an acute symptomatic inhalation event such as fire, mixing cleaning
products, or chemical spills (RR=3.3, 95% CI 1.0–11.1, p=0.051). The population-attributable risk for adult asthma due to occupational exposures ranged from 10% to 25%, equivalent to an incidence of new-onset occupational asthma of 250–300 cases per million people per year. Occupational exposures account for a substantial proportion of adult asthma incidence. The increased risk of asthma after inhalation accidents suggests that workers who have such accidents should be monitored closely.


The aim of this study was to assess dual renin system intervention with the maximum recommended doses of aliskiren and valsartan, compared with each drug alone in patients with hypertension. In this double-blind study, 1797 patients with hypertension (mean sitting diastolic blood pressure 95–109 mmHg and 8-h daytime ambulatory diastolic blood pressure ≥90 mmHg) were randomly assigned to receive once-daily aliskiren 150 mg (n=437), valsartan 160 mg (455), a combination of aliskiren 150 mg and valsartan 160 mg (446), or placebo (459) for 4 weeks, followed by forced titration to double the dose to the maximum recommended dose for another 4 weeks. The primary endpoint was change in mean sitting diastolic blood pressure from baseline to week 8 endpoint. Analyses were done by intention to treat. 196 (11%) patients discontinued study treatment before the end of the trial (63 in the placebo group, 53 in the aliskiren group, 43 in the valsartan group, and 37 in the aliskiren/valsartan group), mainly due to lack of therapeutic effect. At week 8 endpoint, the combination of aliskiren 300 mg and valsartan 320 mg lowered mean sitting diastolic blood pressure from baseline by 12.2 mmHg, significantly more than either monotherapy (aliskiren 300 mg 9.0 mmHg decrease, p<0.0001; valsartan 320 mg, 9.7 mmHg decrease, p<0.0001), or with placebo (4.1 mmHg decrease, p<0.0001). Rates of adverse events and laboratory abnormalities were similar in all groups. The combination of aliskiren and valsartan at maximum recommended doses provides significantly greater reductions in blood pressure than does monotherapy with either agent in patients with hypertension, with a tolerability profile similar to that with aliskiren and valsartan alone.


Whether cannabis can cause psychotic or affective symptoms that persist beyond transient intoxication is unclear. We systematically reviewed the evidence pertaining to cannabis use and occurrence of psychotic or affective mental health outcomes. We searched Medline, Embase, CINAHL, PsycINFO, ISI Web of Knowledge, ISI Proceedings, ZETOC, BIOSIS, LILACS, and MEDCARIB from their inception to September, 2006, searched reference lists of studies selected for inclusion, and contacted experts. Studies were included if longitudinal and population based. 35 studies from 4804 references were included. Data extraction and quality assessment were done independently and in duplicate. There was an increased risk of any psychotic outcome in individuals who had ever used cannabis (pooled adjusted odds ratio=1.41, 95% CI 1.20–1.65). Findings were consistent with a dose-response effect, with greater risk in people who used cannabis most frequently (2.09, 1.54–2.84). Results of analyses restricted to studies of more clinically relevant psychotic disorders were similar. Depression, suicidal thoughts, and anxiety outcomes were examined separately. Findings for these outcomes were less consistent, and fewer attempts were made to address non-causal explanations, than for psychosis. A substantial confounding effect was present for both psychotic and affective outcomes. The evidence is consistent with the view that cannabis increases risk of psychotic outcomes independently of confounding and transient intoxication effects, although evidence for affective outcomes is less strong.


Female-controlled methods of HIV prevention are urgently needed. We assessed the effect of provision of latex diaphragm, lubricant gel, and condoms (intervention), compared with condoms alone (control) on HIV seroincidence in women in South Africa and Zimbabwe. We did an open-label, randomised controlled trial in HIV-negative, sexually active women recruited from clinics and
Acute lymphoblastic leukaemia in infants younger than 1 year is rare, and infants with the disease have worse outcomes than do older children. We initiated an international study to investigate the effects of a new hybrid treatment protocol with elements designed to treat both acute lymphoblastic leukaemia and acute myeloid leukaemia, and to identify any prognostic factors for outcome in infants. We also did a randomised trial to establish the value of a late intensification course. Patients aged 0–12 months were enrolled by 17 study groups in 22 countries between 1999 and 2005. Eligible patients were stratified for risk according to their peripheral blood response to a 7-day prednisone prophase, and then given a hybrid regimen based on the standard protocol for acute lymphoblastic leukaemia, with some elements designed for treatment of acute myeloid leukaemia. Before the maintenance phase, a subset of patients in complete remission were randomly assigned to receive either standard treatment or a more intensive chemotherapy course with high-dose cytarabine and methotrexate. The primary outcomes were event-free survival (EFS) for the initial cohort of patients and disease-free survival (DFS) for the patients randomly assigned to a treatment group. Data were analysed on an intention-to-treat basis. In the 482 enrolled patients who underwent hybrid treatment, 260 (58%) were in complete remission at a median follow-up of 38 (range 1–78) months, and EFS at 4 years was 47·0% (SE 2·6, 95% CI 41·9–52·1). Of 445 patients in complete remission after 5 weeks of induction treatment, 191 were randomised: 95 patients to receive a late intensification course, and 96 to a control group. At a median follow-up of 42 (range 1–73) months, 60 patients in the treatment group and 57 controls were disease-free. DFS at 4 years did not differ between the two groups (60·9% [SE 5·2] for treatment group vs 57·0% [SE 5·5] for controls; p=0·81). During the intensification phase, of 71 patients randomly assigned to the treatment group, and for whom toxicity data were available, 35 (49%) had infections, 21 (30%) patients had mucositis, 22 (31%) patients had toxic effects on the liver, and 2 (3%) had neurotoxicity. All types of rearrangements in the (mixed lineage leukaemia) MLL gene, very high white blood cell count, age of younger than 6 months, and a poor response to the prednisone prophase were independently associated with inferior outcomes. Patients treated with our hybrid protocol, and especially those who responded poorly to prednisone, had higher EFS than most reported outcomes for treatment of infant ALL. Delayed intensification of chemotherapy did not benefit patients.

SERIES: Psoriasis


Psoriasis, a papulosquamous skin disease, was originally thought of as a disorder primarily of epidermal keratinocytes, but is now recognised as one of the commonest immune-mediated disorders. Tumour necrosis factor α, dendritic cells, and T-cells all contribute substantially to its pathogenesis. In early-onset psoriasis (beginning before age 40 years), carriage of HLA-Cw6 and environmental triggers, such as α-haemolytic streptococcal infections, are major determinants of disease expression. Moreover,
at least nine chromosomal psoriasis susceptibility loci have been identified. Several clinical phenotypes of psoriasis are recognised, with chronic plaque (psoriasis vulgaris) accounting for 90% of cases. Comorbidities of psoriasis are attracting interest, and include impairment of quality of life and associated depressive illness, cardiovascular disease, and a seronegative arthritis known as psoriatic arthritis. A more complete understanding of underlying pathomechanisms is leading to new treatments, which will be discussed in the second part of this Series.


Management of psoriasis begins with identification of the extent of cutaneous disease. However, a holistic, contractual approach to treatment is encouraged, with particular reference to psychosocial disability and quality-of-life issues. The presence of psoriasis on palms, soles, body folds, genitals, face, or nails, and concomitant joint disease, are also important when considering treatment options. An evidence-based approach is essential in delineating differences between the many available treatments. However, archaic approaches, especially combinational ones, are routinely used by some clinicians, with inadequate prospective or comparative evidence. Treatments currently available are: topical agents used predominantly for mild disease and for recalcitrant lesions in more severe disease; phototherapy for moderate disease; and systemic agents including photochemotherapy, oral agents, and newer injectable biological agents, which have revolutionised the management of severe psoriasis. Other innovative treatments are undergoing clinical studies, with the aim of maintaining safe, long-term control of the condition.

SEMINAR


Chronic myeloid leukaemia (CML) was the first neoplastic disease for which knowledge of the genotype led to a rationally designed therapy. As a result of its well known pathophysiology, straightforward diagnosis, well established prognostic factors, and treatment for the cause of disease, CML has been studied to an extent that far exceeds that expected from its frequency, and serves as a model disease for other cancers.

Imatinib, an inhibitor of BCR-ABL tyrosine kinase, has revolutionised treatment of this disease, and is now recommended as standard treatment for chronic-phase CML. Interferon alfa is an acceptable alternative treatment in the early chronic phase for patients who do not tolerate imatinib. If imatinib treatment fails, allogeneic stem-cell transplantation, a dose increase of imatinib, or new drugs are recommended. Up to 87% of patients achieve complete cytogenetic remission, therefore we provide guidance for monitoring disease status. Many trials of new drugs and combination therapies that include imatinib are underway.

REVIEW


In-vitro fertilisation has been done for nearly 30 years; in developed countries at least 1% of births are from assisted reproductive therapies (ART). These children now represent a substantial proportion of the population but little is known about their health. Some of the morbidity associated with ART does not result from the techniques but from the underlying health risks of being subfertile. Much of the amplified risk associated with ART is related to high birth order. However, risk of intrauterine and subsequent perinatal complications is enhanced after ART, and urogenital malformations can be present in boys, even in singleton infants. No increase in discord or other difficulties within families has been recorded. Long-term follow-up of children born after ART to reproductive age and beyond is necessary.