

Learning to identify and classify reports of controlled trials in healthcare journals

*examples of various types of study designs
and how they should be classified - illustrated with
MEDLINE abstracts*

Material presented at Cochrane Colloquium,
Cape Town, October 2000

New England Cochrane Center, Providence Office

About this resource

This material was first presented at the Cochrane Colloquium, Cape Town (October 2000). The content of this workshop was created at the NECC@P by **Susan Wieland**, in consultation with **Kay Dickersin** and **Eric Manheimer**.

To ensure there was agreement between the definitions and classifications used by the NECC@P and the UKCC, the material was also reviewed by Maggie Westby, the quality checker at the UKCC. The examples in this resource conform to the study design classification systems used by both Centers.

Please note

For the purpose of this exercise we have used MEDLINE abstracts rather than full-text articles to illustrate issues concerning study design and the coding of trial reports. *Users of this resource should be aware that the coding given in these examples was based solely on the MEDLINE abstract, not the full article.* In general, however, it is not recommended to just review the bibliographic abstract since there is no way of guaranteeing that a review of the full article would result in the same classification code. The abstracts in this resource were chosen to demonstrate certain issues where there is confusion about study design classification, and where the relevant issue(s) were described clearly in the abstract.

Abstracts have been used in this case to facilitate electronic dissemination, to skirt any copyright issues concerning the use of full-text articles, and to derive maximum benefit from the teaching time during the workshop.

If you have any comments or suggestions please contact the New England Cochrane Center, Providence Office by sending an email to cochrane@brown.edu

THE STUDY COMPARES INTERVENTIONS IN HUMAN BEINGS

The study must not be carried out exclusively *in vitro* (UI: 99081249)

The study may be carried out on human parts that will be replaced in living humans, e.g., donor organs or blood (UI: 20374254)

The study may not be carried out exclusively in animals (UI: 20462509)

The study must be carried out on actual human beings, not on a hypothetical cohort or using simulation (UI: 20387177)

The study must be carried out on living human beings, not on cadavers (UI: 20460866)

The study may be carried out on body parts or organs of living humans, such as legs, teeth or eyes (UI: 20285582)

The study may not be carried out on parts that will not be replaced in living humans, such as extracted teeth (UI: 20415954)

The study may compare interventions in groups of humans, such as communities, schools, or medical practices (UI: 20438943)

The study may compare interventions in a single person, if a randomized design is used (UI: 97457113)

THE STUDY IS PROSPECTIVE

The intervention must be planned by investigators before the study begins and the investigators must control which participants are exposed to the intervention (UI: 99289421)

The study may not be a comparison of interventions which were not planned and allocated by the investigators (UI: 99415485)

The study may not compare an intervention planned and allocated by the investigators to an intervention that was not planned and allocated by the investigators. An intervention not planned and allocated by the investigators may be found in a historical cohort comparison group (UI: 99299911) or a concurrent control comparison group (UI: 93092728)

TWO OR MORE INTERVENTIONS ARE COMPARED

The study may compare the conventional intervention to some new intervention (UI: 99361632), one or more active interventions to placebo intervention (UI: 20355093), or two or more interventions to each other (UI: 99370960)

The study may not give all participants the same interventions in the same order (UI: 99073590)

The study may give all participants the same interventions if the order of interventions is randomized for each patient (randomized crossover design). Sometimes this type of study has a Latin square design and the subjects are randomized to lines within the square (UI: 20458991; 99361751), and sometimes the study merely mentions that the order of interventions was random (UI: 20009452)

Interventions may be assigned by group or individual (see third item under RCT on next page)

ASSIGNMENT OF PARTICIPANTS TO INTERVENTIONS IS INTENDED TO BE RANDOM

RCTs

The article may explicitly state that participants were assigned to interventions by means of a random number table or other randomization technique, in which case the article is an RCT (UI: 96254437)

If the article states that participants were randomized, but does not state the method of randomization, it is assumed that randomization took place and the article is an RCT (UI: 20458781)

The study may compare participants who are assigned to interventions by individual or by group (e.g., towns, schools). In the latter case the groups must be randomly assigned to the intervention.

CCTs

The article may explicitly state that participants were assigned to interventions by a quasi-randomization technique, in which case the article is a CCT (UI: 98165441)

If the article states that participants were allocated to intervention groups using a method which we know to be quasi-randomization, such as alternation, coin toss, or medical record number, the article is a CCT (UI: 99192268)

If the article states that participants were allocated to different interventions, but does not specify how the investigators allocated participants to particular interventions, the article is a CCT (UI: 20018615)

N/A

If the article states that participants were randomly selected to participate but does not specify that the participants were allocated to different interventions, the article is not eligible (UI: 20464973)

If the article states that participants were allocated to intervention groups using a method which we know to be neither randomization nor quasi-randomization, the article is not eligible (UI: 99306284)

If the article states that participants were assigned to different interventions for clinical reasons, the article is not eligible (UI: 99294113)

If the article states that participants selected their own interventions, the article is not eligible (UI: 99045523)

If the article states that the intervention and control groups consist of different types of participants, such as sick individuals compared to healthy individuals, the article is not eligible (UI: 99299904) unless both groups receive two or more interventions (UI: 20405166)

If the article states that the intervention group was compared to another group matched to the intervention group, the article is not eligible (UI:99287964) unless the matched groups were constructed before randomization to intervention (UI: 20448559)

HEALTH RELATED INTERVENTIONS ARE STUDIED - THE INTERVENTION MUST BE RELATED TO HEALTH STATUS, HEALTH CARE, OR HEALTH RESEARCH

The intervention may be a drug, surgical, or behavioral prevention instead of an intervention (UI: 20452482)

The intervention may be a screening program (UI:20038969)

The intervention may be a diagnostic instrument, test or technique (UI: 99272801; 99321356; 20065911)

The intervention may be a comparison of dose amounts, dose timing, or titration regimens (UI: 84205507; 99139206; 99357183)

The intervention may be a comparison of the same intervention at two different durations (UI: 99219248)

The intervention may test the effects of drug, surgical, or behavioral interventions upon athletic performance (UI: 99161586)

The intervention may be the medical education of physicians or other health professionals (UI: 99266760; 20108684)

The intervention may be the education of patients or other non-health professionals about health or disease (UI: 20201122)

The intervention may test for changes in psychological or behavioral outcomes which are explicitly related to health (UI: 20011076)

The intervention may be one designed solely to elucidate a biomechanical, pathophysiological or pharmacokinetic relationship related to a disease, an intervention, or athletic performance (UI: 99262549; 99246479; 99283393)

The intervention may test for differences in cost-effectiveness between interventions (UI: 20364413)

The intervention may be designed to determine outcomes related to health research, such as follow-up rates or response rates to a survey (UI: 99281513)

The study may be randomized but be ineligible for inclusion in the Cochrane Library if the intervention is not health related (UI: 98080917)

ISSUES SURROUNDING RANDOMIZED CLINICAL TRIALS

When an article mentions that an RCT is being planned or has begun, the article is considered an RCT (UI: 99030126)

When an article presents baseline data on randomized participants from an RCT, the article is an RCT even though no results of the intervention comparison are presented (UI: 97062279)

When an article presents preliminary results of an RCT, the article is an RCT (UI: 99353496)

When an article presents new data, a new analysis, or new information about the participants, outcome criteria, or some other aspect of a previously published RCT, the article is an RCT (UI: 20041592; 99265687; 98211005)

When an article presents the results of a follow-up to an RCT, such as an open-label extension or a naturalistic follow-up, the article is considered an RCT (UI: 99241873)

PHASE I, PHASE II, PHASE III AND PHASE IV TRIALS

Phase I trials are often dose ranging trials which are done to determine the maximum dose of a new medication that can be safely given to a patient. They usually do not use randomization and are therefore not considered RCTs or CCTs (UI: 20410828). However, when Phase I trials use randomization to compare intervention regimens, they are considered RCTs (UI: 20272000).

Phase II trials are done to test the efficacy of a new medication or intervention. Often they do not use randomization, and are therefore not considered RCTs or CCTs (UI: 20452350). However, Phase II trials which use randomization to compare interventions are considered RCTs (UI: 20302464).

Phase III trials are done to determine the effectiveness and possible adverse reactions for a new intervention. Most Phase III trials are randomized, and this will often be stated explicitly in the title or abstract (UI: 20402471). Phase III trials which do not mention randomization are considered CCTs (UI: 20376330), unless the article explicitly states that the study is not a comparative study (UI: 20381479), in which case the trial would not be eligible for inclusion in the Cochrane Library.

Phase IV trials are done to monitor the toxicity and utility of an intervention after the efficacy of the intervention has been proven. Often they do not use randomization, and are therefore not considered RCTs or CCTs (UI: 99379035). However, Phase IV trials which use randomization to compare interventions are considered RCTs (UI: 97306736).

REVIEWS AND META-ANALYSES

Reviews are reports that summarize the knowledge to date about some medical condition or its intervention. Reviews may refer to a series of both published and unpublished trials but do not usually report in detail the results of a new or unpublished RCT or CCT. Unless a review highlights the results of a new RCT or CCT, the review is not considered to be an RCT or CCT (UI: 99424961; 97070483)

Meta-analyses are reviews that use systematic methods to summarize the results of previous studies. Like reviews, meta-analyses rely on a series of both published and unpublished trials but do not usually report in detail the results of a new or unpublished RCT or CCT. Such meta-analyses are not considered to be RCTs or CCTs (UI: 20435210)

Sometimes a meta-analysis or review will be done in conjunction with a new RCT or CCT, in which case the article containing the meta-analysis or review and the new trial would be an RCT or CCT (UI: 95230091)

EXAMPLES:

AU: Quinlan, D. P. Jr, Rameshwar, P., Qian, J., Maloof, P. B., Mohr, A. M., Hauser, C. J., and Livingston, D. H.

TI: Effect of hypoxia on the hematopoietic and immune modulator preprotachykinin-I

SO: Arch Surg

YR: 1998 Dec. VL: 133 NO: 12 PG: 1328-34

UI: 99081249

AB: OBJECTIVES: To determine the effect of hypoxia on bone marrow mononuclear cells (BMMCs) and their ability to proliferate into granulocyte-macrophage colony-forming units (CFU-GMs) and erythroid burst-forming units (BFU-Es) and to determine the role of the neuroimmune and hematopoietic mediator, substance P. DESIGN: Controlled *in vitro* study. SETTING: University research laboratory. MATERIALS: Bone marrow aspirates were obtained from the posterior iliac crests of healthy volunteers after obtaining informed consent. INTERVENTIONS: The BMMCs were divided into the following groups: (1) normoxia, (2) two hours of hypoxia, and (3) six hours of hypoxia. Additional BMMCs were purified before the period of hypoxia, while others were incubated with neurokinin (NK) receptor antagonists. In other experiments, bone marrow stroma was grown to confluence and randomized to the following groups: (1) normoxia, (2) hypoxia, (3) normoxia and interleukin (IL) 1, and (4) hypoxia and IL-1. All groups were cultured for 2, 6, 12, or 24 hours. MAIN OUTCOME MEASURES: The formation of CFU-GMs and BFU-Es was measured after 10 to 14 days of incubation of the BMMCs. The messenger RNA of the preprotachykinin-I (PPT-I) gene and the NK-1 and NK-2 receptors was detected by using semiquantitative reverse transcriptase-polymerase chain reaction or Northern blot analysis on bone marrow stroma. The immunoreactivity of substance P in bone marrow stroma was measured by competitive enzyme-linked immunosorbent assay. RESULTS: Hypoxia resulted in a 110% increase in the number of CFU-GMs and a 78% increase in the number of BFU-E colonies at 6 hours (both $P < .05$). Elimination of the stromal elements by purification abrogated the increase in colony formation to nonhypoxic levels. Hypoxia induced PPT-I gene expression at 24 hours; however, no PPT-I expression was found in the hypoxic group incubated with IL-1. The receptor, NK-1, was found to be equal in both hypoxic groups; NK-2 was found to have a 4-fold increase in the hypoxia and IL-1 group over the hypoxia alone group and normoxia and IL-1 group. The levels of substance P immunoreactivity were found to be similar in all groups. Incubation of BMMCs with NK receptor antagonists to NK-1 alone or NK-1 and NK-2 decreased the number of CFU-GM and BFU-E colonies similar to the level in controls. CONCLUSIONS: These results indicate that hypoxia has a role in the proliferation and control of CFU-GMs and BFU-Es. This control seems to be mediated through the bone marrow stroma and modulated by NK receptors and induction of PPT-I. The neuropeptide, substance P, probably has a role but is clearly not the only mediator involved.

Article classification: N/A

This is an example of a randomized study which is carried out exclusively *in vitro* and therefore is not eligible for inclusion in the Cochrane Library. A controlled study which is

done *in vitro* and in living human beings, however, could be eligible for inclusion in the Cochrane Library.

AU: Polyak, M. M., Arrington, B. O., Kapur, S., Stubenbord, W. T., and Kinkhabwala, M.

TI: Glutathione supplementation during cold ischemia does not confer early functional advantage in renal transplantation

SO: Transplantation

YR: 2000 July VL: 70 NO: 1 PG: 202-5

UI: 20374254

AB: BACKGROUND: Reduced glutathione (GSH), a component of University of Wisconsin (UW) solution, is reported to oxidize during storage. Consequently the commercial manufacturer of UW recommends the supplemental addition of GSH to UW before utilization. We investigated the influence of supplemental GSH during cold ischemia on early renal allograft function. METHODS: One hundred kidneys were locally procured from heart-beating donors, preserved in our laboratory, and transplanted during an 18-month period. Selected donor, preservation, and outcome characteristics were collected and compared by presence of supplemental GSH and method of preservation. All kidneys were randomized to receive 3.0 mM supplemental GSH to perfusate or no supplementation (control) and were preserved by either cold storage (CS) in UW or machine perfused (MP) in UW-machine perfusate solution (MPS). During MP, perfusion characteristics (flow, resistance, perfusate electrolytes, and pH) were serially measured. RESULTS: There were no significant differences among the groups when the donor characteristics of age, serum creatinine, and intra-operative urine output were compared. Preservation characteristics were similar among the groups with the exception of cold ischemia time, which was longer in the MP group compared to CS (26.1 h vs. 21.9 h, $P=0.03$). When compared with CS, kidneys preserved by MP exhibited a 33.4% increase in immediate function (93% vs. 62%, $P=0.01$), a corresponding 29.4% decrease in the incidence of delayed graft function (10% vs. 34%, $P=0.02$), and a 10% improvement in short-term (6-month) graft survival (98% vs. 88%, $P=0.02$). The addition of GSH supplementation to perfusate resulted in no significant differences in graft outcomes. CONCLUSIONS: Despite recommendations by the manufacturer that UW solution be routinely supplemented with GSH, supplemental GSH does not influence early renal allograft function. Our data suggest that a far greater beneficial impact on early graft function is achieved by machine perfusion. We conclude that GSH supplementation of commercially available UW is not necessary.

Article classification: RCT

This is an example of a randomized study carried out in donor organs. Because donor organs will be placed into the bodies of living human beings, the study is eligible for inclusion in the Cochrane Library.

AU: Robertson, C. L., Clark, R. S., Dixon, C. E., Alexander, H. L., Graham, S. H., Wisniewski, S. R., Marion, D. W., Safar, P. J., and Kochanek, P. M.

TI: No long-term benefit from hypothermia after severe traumatic brain injury with secondary insult in rats

SO: Crit Care Med

YR: 2000 Sept. VL: 28NO: 9 PG: 3218-23
UI: 20462509

AB: OBJECTIVES: To evaluate the effect of application of transient, moderate hypothermia on outcome after experimental traumatic brain injury (TBI) with a secondary hypoxicemic insult. DESIGN: Prospective, randomized study. SETTING: University-based animal research facility. SUBJECTS: Male Sprague-Dawley rats. INTERVENTIONS: All rats were subjected to severe TBI followed by 30 mins of moderate hypoxemia, associated with mild hypotension. Rats were randomized to three groups: a) normothermia (37 degrees C + 0.5 degrees C); b) immediate hypothermia (32 degrees C +/- 0.5 degrees C initiated after trauma, before hypoxemia); and c) delayed hypothermia (32 degrees C +/- 0.5 degrees C after hypoxemia). The brain temperature was controlled for 4 hrs after TBI and hypoxemia. MEASUREMENTS AND MAIN RESULTS: Animals were evaluated after TBI for motor and cognitive performance using beam balance (days 1-5 after TBI), beam walking (days 1-5 after TBI), and Morris Water Maze (days 14-18 after TBI) assessments. On day 21 after TBI, rats were perfused with paraformaldehyde and brains were histologically evaluated for lesion volume and hippocampal neuron counts. All three groups showed marked deficits in beam balance, beam walking, and Morris Water Maze performance. However, these deficits did not differ between groups. There was no difference in lesion volume between groups. All animals had significant hippocampal neuronal loss on the side ipsilateral to injury, but this loss was similar between groups. CONCLUSIONS: In this rat model of severe TBI with secondary insult, moderate hypothermia for 4 hrs posttrauma failed to improve motor function, cognitive function, lesion volume or hippocampal neuronal survival. Combination therapies may be necessary in this difficult setting.

Article classification: N/A

This is an example of a study which is carried out exclusively in animals and is therefore not eligible for inclusion in the Cochrane Library. A study which is carried out in animals and in human beings, however, could be eligible for inclusion in the Library.

AU: Norman, G. R. and Daya, S.

TI: The alternating-sequence design (or multiple-period crossover) trial for evaluating treatment efficacy in infertility

SO: Fertil Steril

YR: 2000 Aug. VL: 74NO: 2 PG: 319-24

UI: 20387177

AB: OBJECTIVE: To determine whether a constant-sequence or an alternating-sequence design is better for the evaluation of infertility treatment efficacy when multiple cycles of treatment are undertaken. DESIGN: A simulation exercise using analytical methods. SETTING: University medical center. PATIENT(S): A hypothetical, heterogeneous population of infertile patients participating in a randomized trial comparing an experimental treatment, with effectiveness of 2.0, to no treatment. INTERVENTION(S): Comparison of a constant-sequence design in which the subject receives the same intervention or the alternating-sequence design in which experimental and control treatments are crossed over after each successive cycle.

MAIN OUTCOME MEASURE(S): Relative risks of pregnancy per cycle and overall after a maximum of five cycles of treatment. **RESULT(S):** With both designs, the pregnancy rates in experimental and control groups showed a consistent decrease with each successive cycle. The overall effectiveness in the constant-sequence design was underestimated at 1.83, whereas in the alternating-sequence design it was overestimated at 2.06. However, by restricting the analysis in the latter design only to the odd-numbered cycles, the relative risk was precisely correct at 2.00. **CONCLUSION(S):** When multiple cycles of treatment are undertaken to evaluate the efficacy of infertility therapy, the alternating-sequence design with restriction of the analysis to only the odd-numbered treatment cycles provides an unbiased estimation of the treatment effect.

Article classification: N/A

This is an example of a study which is hypothetical. It has not been carried out in real human beings, and therefore it is not eligible for inclusion in the Cochrane Library.

AU: Keller, C., Brimacombe, J., Kleinsasser, A., and Loekinger, A.

TI: Does the ProSeal Laryngeal Mask Airway Prevent Aspiration of Regurgitated Fluid?

SO: Anesth Analg

YR: 2000 Oct. VL: 91 NO: 4 PG: 1017-1020

UI: 20460866

AB: In this randomized, cross-over cadaver study, we determined whether a new airway device, the ProSeal laryngeal mask airway (PLMA; Laryngeal Mask Company, Henley-on-Thames, UK), prevents aspiration of regurgitated fluid. We studied five male and five female cadavers (6-24 h postmortem). The infusion set of a pressure-controlled, continuous flow pump was inserted into the upper esophagus and ligated into place. Esophageal pressure (EP) was increased in 2-cm H₂O increments. This was performed without an airway device (control) and over a range of cuff volumes (0-40 mL) for the classic laryngeal mask airway (LMA), the PLMA with the drainage tube clamped (PLMA clamped) and unclamped (PLMA unclamped). The EP at which fluid was first seen with a fiberoptic scope in the hypopharynx (control), above or below the cuff, or in the drainage tube, was noted. Mean EP at which fluid was seen without any airway device was 9 (range 8-10) cm H₂O. EP at which fluid was seen was always higher for the PLMA clamped and LMA compared with the control (all, P: < 0.0001). The mean EP at which fluid was seen for the PLMA unclamped was similar to the control at 10 (range 8-13) cm H₂O. For the PLMA unclamped, fluid appeared from the drainage tube in all cadavers at 10-40 mL cuff volume and in 8 of 10 cadavers at zero cuff volume. Mean EP at which fluid was seen above the cuff was similar for the PLMA clamped and LMA at 0-30 mL cuff volume, but was higher for PLMA clamped at 40-mL cuff volume (81 vs 48 cm H₂O, P: = 0.006). Mean EP at which fluid was seen below the cuff was similar at 0-10 mL cuff volume, but was higher for the PLMA clamped at 20, 30, and 40 mL cuff volume (62, 68, 73 vs 46, 46, 46 cm H₂O, respectively, P: < 0.04). For the PLMA clamped and the LMA, fluid appeared simultaneously above and below the cuff at all cuff volumes. We concluded that in the cadaver model, the correctly placed PLMA allows fluid in the esophagus to bypass the pharynx and mouth when the drainage tube is open. Both the LMA, and PLMA with a closed drainage tube, attenuate

liquid flow between the esophagus and pharynx. This may have implications for airway protection in unconscious patients. Implications: The correctly placed ProSeal laryngeal mask airway allows fluid in the esophagus to bypass the oropharynx in the cadaver model. This may have implications for airway protection in unconscious patients.

Article classification: N/A

This is an example of a randomized study which is carried out in cadavers and therefore is not eligible for inclusion in the Cochrane Library.

AU: Shumayrikh, N. M. and Adenubi, J. O.

TI: Clinical evaluation of glutaraldehyde with calcium hydroxide and glutaraldehyde with zinc oxide eugenol in pulpotomy of primary molars

SO: Endod Dent Traumatol

YR: 1999 Dec. VL: 15 NO: 6 PG: 259-64

UI: 20285582

AB: The objectives of this study were to clinically evaluate the effectiveness of 2% buffered glutaraldehyde in pulpotomies of human primary molars and to compare the success rate of glutaraldehyde with calcium hydroxide and glutaraldehyde with zinc oxide eugenol as dressing material on the radicular pulp. Pulpotomies were completed on 61 primary molars in 19 children. The teeth were divided into two groups by random allocation. One group had a dressing of zinc oxide-eugenol base (IRM) incorporated with one drop of 2% buffered glutaraldehyde while the other group had a dressing of calcium hydroxide base incorporated with one drop of 2% buffered glutaraldehyde after the initial placement of 2% buffered glutaraldehyde on cotton pellet for 3 min. All teeth had light-curing compomer (Dyract) placed over the dressing material followed by a stainless steel crown restoration within 1 or 2 weeks after the pulpotomy. Blind clinical and radiographic evaluations of 57 teeth available after 12 months showed a success rate of 92.9% and 73.6% respectively. The clinical and radiographic success rates for glutaraldehyde/zinc oxide eugenol pulpotomies were 96.5% and 75.8% respectively while those for glutaraldehyde-calcium hydroxide were 89.2% and 71.4%. There was no statistically significant difference between the two groups either clinically or radiographically. The overall clinical success rate suggested that 2% buffered glutaraldehyde was an effective agent in the pulpotomy of human primary molars.

Article classification: RCT

This is an example of a study in which a body part or parts (in this case, teeth) were randomized to different treatments. Because the parts are within living human beings, the study is eligible for inclusion in the Cochrane Library.

AU: Aggarwal, M., Foley, T. F., and Rix, D.

TI: A comparison of shear-peel band strengths of 5 orthodontic cements

SO: Angle Orthod

YR: 2000 Aug. VL: 70 NO: 4 PG: 308-16

UI: 20415954

AB: The objective of this study was to compare the shear-peel band strength of 5 orthodontic cements using both factory and in-office micro-etched bands. The 5

orthodontic cements evaluated were a zinc phosphate (Fleck's Cement), 2 resin-modified glass ionomer cements (RMGI)(3M Multicure glass ionomer and Optiband), and 2 polyacid-modified composite resin cements (PMCR)(Transbond Plus and Ultra Band Lok). Salivary contamination was examined with a polyacid-modified composite resin (Transbond Plus). Two hundred and eighty extracted human molar teeth were embedded in resin blocks and each was randomly assigned to the following 7 groups: 6 groups with factory etched bands, 5 cement groups and salivary contaminated group, and 1 in-office micro-etched group. The cemented teeth were put in deionized water at 37 degrees C for 30 days and thermocycled for 24 hours. The force required to break the cement bond was used as a measure of shear-peel band retention. With the use of an Instron testing machine, a shear-peel load was applied to each cemented band. Data were analyzed with a one-way analysis of variance (ANOVA) with a Tukey test for the multiple comparisons. The RMGIs and PMCRs demonstrated significantly greater shear-peel band strengths compared to the zinc phosphate cement. No statistically significant differences were noted between the RMGI cement and PMCR cements and within the RMGI groups, however, there was a statistically significant difference within the PMCR groups. Significantly lower band strengths were noted with the saliva contaminated PMCR cement group (Transbond Plus) and the inpractice sandblasted PMCR group. Both RMGIs and PMCRs were found to demonstrate favorable banding qualities. The lower band strength with saliva-contaminated bands suggests that moisture control is critical when using a PMCR. The variability noted in the in-office micro-etched bands might be technique related.

Article classification: N/A

This is an example of a study carried out in extracted teeth. Because extracted teeth are not part of living human beings, nor intended to be implanted in living human beings, the article is not eligible for inclusion in the Cochrane Library.

AU: Duan, N., Fox, S. A., Derose, K. P., and Carson, S.

TI: Maintaining mammography adherence through telephone counseling in a church-based trial

SO: Am J Public Health

YR: 2000 Sept. VL: 90NO: 9 PG: 1468-71

UI: 20438943

AB: OBJECTIVES: This study assessed the effectiveness of telephone counseling in a church-based mammography promotion intervention trial. METHODS: Thirty churches were randomized to telephone counseling and control conditions; telephone interview data were used in assessing intervention effects on mammography adherence.

Separate analyses were conducted for baseline-adherent participants (maintaining adherence) and baseline-nonadherent participants (conversion to adherence).

RESULTS: Year 1 follow-up data indicated that the telephone counseling intervention maintained mammography adherence among baseline-adherent participants and reduced the nonadherence rate from 23% to 16%. CONCLUSIONS: Partnerships between the public health and faith communities are potentially effective conduits to promote maintenance of widely endorsed health behaviors such as regular cancer screening.

Article classification: RCT

This is an example of a trial in which randomization was not carried out individual by individual, but group by group. In this case, the groups were churches, but other examples might be schools, medical practices, or entire communities. These studies are eligible for inclusion in the Cochrane Library.

AU: Speich, R., Boehler, A., Russi, E. W., and Weder, W.

TI: A case report of a double-blind, randomized trial of inhaled steroids in a patient with lung transplant bronchiolitis obliterans

SO: Respiration

YR: 1997 VL: 64 NO: 5 PG: 375-80

UI: 97457113

AB: Lung transplant bronchiolitis obliterans syndrome (BOS) is the most significant long-term cause of morbidity and mortality after lung transplantation. Although augmented immunosuppression is used by most centers, reported on treatment to reverse BOS are largely anecdotal. We performed a double-blind, randomized, controlled trial (RCT) with ten treatment pairs of 2 weeks duration each comparing inhaled fluticasone propionate (2 x 1,000 micrograms/day) with placebo in a patient with BOS grade 2 who previously showed an improvement in lung function after inhaled steroids. The Baseline Dyspnea Index and the Modified Medical Research Council Dyspnea Scale showed a significant improvement during fluticasone treatment compared with the placebo period (2.7 +/- 0.2 vs. 2.0 +/- 0.3; p = 0.043; and 1.7 +/- 0.2 vs. 2.4 +/- 0.2; p = 0.043). The patient correctly identified fluticasone and placebo, respectively, in eight of ten trial pairs (p = 0.016). The values of forced expiratory volume in 1 s were significantly higher during the fluticasone period (1,207 +/- 10 ml; 95% confidence interval, CI, 1,187-1,227 ml) compared to the placebo period (1,150 +/- 6 ml; 95% CI 1,138-1,162 ml; p = 0.0012). In conclusion, this n-of-1 RCT suggests the efficacy of high-dose inhaled fluticasone in our patient with lung transplant BOS. We propose to conduct a multicenter RCT of high-dose inhaled steroids. Until further data are available, this treatment modality should be offered to patients with lung transplant BOS.

Article classification: RCT

This is an example in which a randomized design is used with a single subject. This is a relatively unusual study design, however it is eligible for inclusion in the Cochrane Library.

AU: Busse, W., Nelson, H., Wolfe, J., Kalberg, C., Yancey, S. W., and Rickard, K. A.

TI: Comparison of inhaled salmeterol and oral zafirlukast in patients with asthma

SO: J Allergy Clin Immunol

YR: 1999 June VL: 103 NO: 6 PG: 1075-80

UI: 99289421

AB: BACKGROUND: Salmeterol, a long-acting beta2 -agonist, and zafirlukast, a leukotriene receptor antagonist, are both indicated for the treatment of asthma in adolescent and adult patients. OBJECTIVE: We sought to compare the effect of 4

weeks of treatment with inhaled salmeterol xinafoate versus oral zafirlukast in the treatment of persistent asthma. **METHODS:** This was a randomized, double-blind, double-dummy, parallel-group, multicenter clinical trial. Patients, over 80% of whom were on a concurrent inhaled corticosteroid regimen, were treated for 4 weeks with either inhaled salmeterol xinafoate 42 microgram twice daily administered by means of a metered-dose inhaler or oral zafirlukast 20 mg twice daily. The primary efficacy measure was morning peak expiratory flow (PEF); secondary efficacy measures included evening PEF, asthma symptom scores, supplemental albuterol use, nighttime awakenings, sleep symptoms, asthma exacerbations, and FEV1. **RESULTS:** Both inhaled salmeterol and oral zafirlukast resulted in within-group improvements from baseline in measures of pulmonary function, asthma symptoms, and supplemental albuterol use. Salmeterol treatment resulted in significantly greater improvements from baseline compared with zafirlukast for most efficacy measurements, including morning PEF (29.6 vs 13.0 L/min; $P \leq .001$), percentage of symptom-free days (22.4% vs 8.8%; $P \leq .001$), and percentage of days and nights with no supplemental albuterol use (30.5% vs 11.3%; $P \leq .001$). There were no differences in safety profiles as assessed by adverse event monitoring. **CONCLUSION:** In patients with persistent asthma, most of whom were concurrently using inhaled corticosteroids, treatment with inhaled salmeterol provided significantly greater improvement than oral zafirlukast in overall asthma control over the 4-week treatment period.

Article classification: RCT

This is an example of a study in which investigators planned the study prospectively. The study was designed, patients were enrolled, and patients were then randomly allocated by the investigators to one of the two different treatments. This study is clearly eligible for inclusion in the Cochrane Library.

AU: Chan, A. and Wong, A.

TI: Is combined chemotherapy and radiation therapy equally effective as surgical resection in localized esophageal carcinoma?

SO: Int J Radiat Oncol Biol Phys

YR: 1999 Sept. VL: 45NO: 2 PG: 265-70

UI: 99415485

AB: **PURPOSE:** This is a retrospective cohort comparison of combined chemotherapy and radiation versus esophagectomy in nonmetastatic esophageal cancers. **METHODS AND MATERIALS:** Between 1984 and 1994, 82 patients received concurrent chemotherapy and radiation as their primary treatment. Their treatment consisted of 50-60 Gy of radiation in 20-30 fractions over 4-6 weeks, concurrent with bolus mitomycin C (8 mg/m²) on day 1, 5-fluorouracil (5-FU) infusion (20 mg/kg/day) +/- leucovorin (20 mg/m²/day) on days 1-4 and 22-25. This group was compared to another cohort of 81 patients who had esophagectomy. Both groups were restaged according to the 1983 AJCC clinical staging system and there was more clinical Stage III disease in the chemoradiation group, 30% versus 16%. **RESULTS:** The complete response rate was 68% after chemoradiation (by clinical assessment) and 83% for esophagectomy (by pathological assessment). At 5 years, the local relapse rate was 59% for chemoradiation and 51% for esophagectomy. The 5-year disease-free rate and survival

were 23% and 25% for chemoradiation, and 21% and 23% for esophagectomy respectively. There was no significant difference in the disease control and survival between the two treatments. The pretreatment AJCC clinical stage was a strong prognosticator of outcome. The 5-year survival was 55% for Stage I, 16% for Stage II, and 8% for Stage III ($p = 0.00003$). CONCLUSION: Combined chemotherapy and radiation appeared to be as effective as esophagectomy in localized esophageal cancer.

Article classification: N/A

This is an example of a study in which the investigators did not plan and carry out a prospective study. The study compares results of two different treatments which were carried out in previous years. The phrase "retrospective cohort comparison" make it clear that this study is not prospective, and therefore is not eligible for inclusion in the Cochrane Library.

AU: Carel, J. C., Roger, M., Ispas, S., Tondu, F., Lahlou, N., Blumberg, J., and Chaussain, J. L.

TI: Final height after long-term treatment with triptorelin slow release for central precocious puberty: importance of statural growth after interruption of treatment. French study group of Decapeptyl in Precocious Puberty

SO: J Clin Endocrinol Metab

YR: 1999 June VL: 84 NO: 6 PG: 1973-8

UI: 99299911

AB: The impact of treatment of central precocious puberty (CPP) with GnRH agonists on final statural height (FH) remains controversial, and guidelines on the optimal time point for interruption of these treatments have not been established. We analyzed the long term results of 58 girls and 8 boys uniformly treated with triptorelin slow release formulation (Decapeptyl, triptorelin-SR) for CPP and compared their FH with predicted height before treatment and with the FH of a historical group of patients not treated with GnRH agonist. The FH SD score was close to 0 and was not different from the genetic target height. In girls, FH was improved by 4.8 +/- 5.8 cm compared with predicted height before treatment and by 8.3 cm by comparison with a historical group. In boys, comparison with a historical group revealed a 13.7-cm improvement, whereas predicted height before treatment was similar to FH. Three variables were independently associated with FH in girls: the bone age/statural age ratio at the onset of treatment (negatively), the height SD score at the end of treatment, and the posttreatment growth spurt (delta FH - height at the end of treatment). The influence of the posttreatment growth spurt, itself dependent on age and bone age at the interruption of treatment, suggests that continuing treatment beyond the age of 11 yr in girls does not improve and could actually decrease FH. This point should be evaluated in a formal controlled trial.

Article classification: N/A

This is an example of a study in which the results of a planned intervention are compared to results in a historical cohort group. Because the comparison group was

not allocated to its treatment by the study investigators, the study is not a controlled comparison and does not qualify for inclusion in the Cochrane Library.

AU: Thomas, S., Raman, R., Idikula, J., and Brahmadathan, N.

TI: Alterations in oropharyngeal flora in patients with a nasogastric tube: a cohort study

SO: Crit Care Med

YR: 1992 Dec. VL: 20NO: 12 PG: 1677-80

UI: 93092728

AB: OBJECTIVE: To determine whether or not the presence of a nasogastric tube causes a change in the bacterial flora in the oropharynx. STUDY DESIGN: Cohort (prospective) design with concurrent control. SETTING: General Surgical and Ear, Nose, and Throat Units of a tertiary care hospital. PATIENTS: Sixteen patients with and 14 patients without a nasogastric tube. INTERVENTIONS: Patients scheduled to undergo surgery under general anesthesia with endotracheal intubation were eligible for inclusion in the study. From these patients, a study cohort of 16 consecutive patients who were to have nasogastric tube intubation and 14 patients who were not to have nasogastric intubation were enrolled. All patients had a high oropharyngeal swab taken for bacteriologic culture just before surgery. The swab of the oropharynx for culture was repeated after 48 to 72 hrs. The type of organism grown was identified and compared between and within the two groups. RESULTS: There was a significant increase in the frequency of colonization of the oropharynx by pathogenic Gram-negative bacteria after 48 to 72 hrs of nasogastric intubation in comparison with the preintubation level ($p < .01$) as well as in comparison with the group that did not have nasogastric intubation ($p < .001$). The pathogens included Pseudomonas, Klebsiella, Proteus and Escherichia coli. There was also a tendency for suppression of normal flora. There was no significant change in the flora of the control group of patients who did not have nasogastric intubation. The two groups were comparable with respect to age, gender, severity of underlying illness, and use of prophylactic perioperative antibiotics. CONCLUSIONS: The presence of nasogastric tubes in patients predisposes to colonization by Gram-negative pathogenic bacteria within 48 to 72 hrs.

Article classification: N/A

This is an example of a study in which all the participants received the treatments during the same time period, and were followed prospectively by the investigators, but the participants were not randomly allocated to receive one of the two treatments. A prospective design does not necessarily entail investigator control over allocation to treatment. This study is not eligible for inclusion in the Cochrane Library.

AU: Vecchioli Scaldazza, A., Celi, G., De Franco, A., Parrella, A., Minordi, L. M., and Marano, P.

TI: [Intestinal preparation for colon enema with fleet sodium phosphate: comparative study with the conventional method]

SO: Radiol Med (Torino)

YR: 1999 May VL: 97NO: 5 PG: 354-9

UI: 99361632

AB: PURPOSE: To evaluate the possible optimization of a well-tolerated and versatile method of intestinal preparation able to adequately free the lumen and consequently

improve diagnostic results with a lower risk of prolonged hospital stay for incorrectly prepared patients. MATERIAL AND METHODS: We examined 40 patients, namely 20 men (mean age 70 years, range 52-87) and 20 women (mean age 68 years, range 49-81) referred to the Institute of Radiology of the Università Cattolica del Sacro Cuore, Gastrointestinal tract Unit, to undergo double contrast colonic enema. The patients were divided into two groups by one-to-one randomization: group 1 was prepared with the conventional method and group 2 with the new protocol for intestinal preparation. On the two days before the examination a low-residue diet was administered; the day before the examination a phial of Fosfo-soda fleet was administered in two times (at 8 am and 4.30 pm), which was diluted with half a glass of water. Bread, pasta and vegetables were strictly forbidden at lunch and soup or milk at supper; the patients were fasted on the examination day. Two evaluations were performed: one to assess tolerance to the preparation and the other, a radiographic study, to assess the grade of intestinal preparation, the presence of secretions/bubbles, and the degree of painting. RESULTS: Of the 20 patients given X-prep, 3 had to discontinue it and 4 exhibited severe side-effects, but completed the treatment; tolerance was satisfactory in the remaining 13 patients. The grade of intestinal preparation, the presence of secretions/bubbles, and the degree of painting were considered satisfactory in 9, 17 and 16 patients respectively. None of the patients given Fosfo-soda fleet had to discontinue it and tolerance was satisfactory in 19 patients. The grade of intestinal preparation, the presence of secretions/bubbles, and the degree of painting were considered satisfactory in 15, 18 and 18 patients respectively. The statistical analysis of all data was performed with Wilcoxon test. DISCUSSION: Intestinal preparation with Fosfo-soda fleet appeared to be definitely better than the conventional method relative to tolerance ($p = .02$, a statistically significant difference), while providing similarly satisfactory data relative to the other parameters. CONCLUSIONS: Our results, coupled with the versatility of Fosfo-soda fleet (possible application in colonoscopy) and its ease of use recommend this preparation not only for inpatients but also for outpatients in whom self-administration is feasible.

Article classification: RCT

This is an example of a randomized trial in which a new intervention is compared to the usual treatment. This study is eligible for inclusion in the Cochrane Library.

AU: Bhakta, B. B., Cozens, J. A., Chamberlain, M. A., and Bamford, J. M.

TI: Impact of botulinum toxin type A on disability and carer burden due to arm spasticity after stroke: a randomised double blind placebo controlled trial

SO: J Neurol Neurosurg Psychiatry

YR: 2000 Aug. VL: 69NO: 2 PG: 217-21

UI: 20355093

AB: OBJECTIVES: After stroke, abnormal arm posture due to spasticity in a functionally useless arm may interfere with self care tasks. In these patients botulinum toxin treatment presents an opportunity to reduce disability. The purpose was to investigate whether reduction in spasticity after botulinum toxin treatment translates into reduction in disability and carer burden. METHODS: Forty patients with stroke with spasticity in a functionally useless arm (median duration 3.1 years) were randomised to receive

intramuscular botulinum toxin type A (BT-A; Dysport) (n=20) or placebo (n=20) in a total dose of 1000 MU divided between elbow, wrist, and finger flexors. Spasticity (using the modified Ashworth scale), muscle power, joint movement, and pain were assessed. Disability and carer burden were measured using an eight item and a four item scale respectively. Two baseline and three post-treatment assessments (weeks 2, 6, and 12) were made. Concurrent treatments as far as possible remained unchanged and not optimised. RESULTS: Disability improved at week 6 with BT-A compared with placebo. This effect, present at week 2, wore off by week 12. Reduction in carer burden was seen at week 6 with BT-A and continued for at least 12 weeks. Forearm flexor spasticity was reduced with BT-A up to 12 weeks after treatment. Although significant improvement in elbow flexor spasticity was seen at week 2 with BT-A compared with placebo, this effect was not evident at weeks 6 and 12. Arm pain was not improved after BT-A. Grip strength was reduced with BT-A. No serious BT-A related adverse effects were reported. CONCLUSION: BT-A is useful for treating patients with stroke who have self care difficulties due to arm spasticity. The decision to treat should also include relief of carer burden. As muscle weakness may occur, its potential impact on functional activities must be assessed before intervention.

Article classification: RCT

This is an example of a randomized controlled study which compares an active treatment to placebo. This study is eligible for inclusion in the Cochrane Library.

AU: Hata, Y., Uchino, J., Asaishi, K., Kubo, Y., Mito, M., Tanabe, T., Ogita, M., and Hirata, K.

TI: UFT and mitomycin plus tamoxifen for stage II, ER-positive breast cancer. Hokkaido ACETBC Study Group

SO: Oncology (Huntingt) VL: 13NO: 7 Suppl 3 PG: 91-5

UI: 99370960

AB: A trial was designed to examine the combination of UFT and mitomycin (Mutamycin) plus tamoxifen (Nolvadex) as postoperative adjuvant therapy in the treatment of patients with stage II, estrogen receptor (ER)-positive primary breast cancer. Mitomycin was administered intravenously at 13 mg/m² on the day of surgery. Patients judged to be ER-positive were randomly allocated to either group A, which received oral tamoxifen 20 mg/day 14 days after surgery for 2 years, or group B, receiving oral UFT 400 mg/day plus tamoxifen 20 mg/day. A total of 219 patients were enrolled in group A, of which 213 (97.3%) were determined to be eligible; 225 patients enrolled in group B and 223 (99.1%) were eligible. The 5-year survival rates were 93.0% for group A and 95.4% for group B, with no significant difference between groups. The 5-year relapse-free survival rates were 83.1% for group A and 90.7% for group B, a significant advantage (P = .020) for the UFT plus tamoxifen group. Combination therapy with mitomycin, tamoxifen, and UFT proved to be an effective postoperative chemoendocrine therapy for stage II, ER-positive breast cancer.

Article classification: RCT

This is an example of a randomized study in which two or more new interventions are compared. The study is eligible for inclusion in the Cochrane Library.

AU: Sayer, J. W., Gutteridge, C., Syndercombe-Court, D., Wilkinson, P., and Timmis, A. D.

TI: Circadian activity of the endogenous fibrinolytic system in stable coronary artery disease: effects of beta-adrenoreceptor blockers and angiotensin-converting enzyme inhibitors

SO: J Am Coll Cardiol

YR: 1998 Dec. VL: 32 NO: 7 PG: 1962-8

UI: 99073590

AB: OBJECTIVES: To examine circadian changes in the sympathovagal balance, the activity of the renin-angiotensin system and hemostatic variables in patients with stable coronary artery disease, and the effects of beta-adrenoreceptor blockade and angiotensin-converting enzyme inhibition. BACKGROUND: Sympathovagal balance and key components of the fibrinolytic system show circadian variability. The effects of beta-adrenergic blocking agents and angiotensin-converting enzyme inhibitors on these autonomic and hemostatic rhythms are not well defined. METHODS: Twenty patients with coronary artery disease underwent 24-h Holter monitoring for heart rate variability and blood sampling (6 hourly for 24 hours) after three consecutive treatment phases, (firstly with placebo, then bisoprolol, and finally quinapril). The effects on sympathovagal balance, hemostatic variables and the renin-angiotensin system activity were measured. RESULTS: The fibrinolytic capacity showed marked circadian variation at the end of the placebo phase ($p = 0.002$), plasminogen activator inhibitor-1 (PAI-1) activity peaking at 06.00 AM when tissue plasminogen activator (tPA) activity was at its nadir. Sympathovagal balance showed a sharp increase at approximately the same time but plasma renin activity did not rise until later in the day. Inspection of the 24-h profiles suggested that bisoprolol reduced sympathovagal balance and the morning peak of PAI-1 activity and antigen, with a small increase in tPA activity, although these changes were not significant. Quinapril produced a substantial rise in renin ($p = 0.01$) but did not significantly affect either PAI-1 or tPA. Sympathovagal balance was unaffected by quinapril. CONCLUSIONS: In patients with stable coronary artery disease, angiotensin-converting enzyme inhibition with quinapril does not affect either sympathovagal balance or the endogenous fibrinolytic system. Our data suggest that the sympathoadrenal system may modify fibrinolytic activity, judged by the response to beta-adrenoreceptor blockade with bisoprolol.

Article classification: N/A

This is an example of a study in which all participants receive the same treatments in the same order. This article is not eligible for inclusion in the Cochrane Library.

AU: Hallikainen, M. A., Sarkkinen, E. S., Gylling, H., Erkkila, A. T., and Uusitupa, M. I.

TI: Comparison of the effects of plant sterol ester and plant stanol ester-enriched margarines in lowering serum cholesterol concentrations in hypercholesterolaemic subjects on a low-fat diet

SO: Eur J Clin Nutr

YR: 2000 Sept. VL: 54 NO: 9 PG: 715-25

UI: 20458991

AB: Objective: To investigate cholesterol-lowering effects of stanol ester (STAEST) and sterol ester (STEEST)-enriched margarines as part of a low-fat diet. Design: According to a Latin square model randomized double-blind repeated measures design with three test margarines and three periods. Setting: Outpatient clinical trial with free-living subjects. Subjects: Thirty-four hypercholesterolaemic subjects completed the study. Interventions: Subjects consumed three rapeseed oil-based test margarines (STAEST, STEEST and control (no added stanols or sterols)) as part of a low-fat diet each for 4 weeks. Results: Mean daily intake of total plant sterols plus stanols was 2.01-2.04 g during the two test margarine periods. In reference to control, serum total cholesterol was reduced by 9.2 and 7.3% with the STAEST and STEEST margarine, respectively ($P < 0.001$ for both). The respective reductions for low-density lipoprotein (LDL) cholesterol were 12.7 and 10.4% ($P < 0.001$). The cholesterol-lowering effects of the test margarines did not differ significantly. The presence of apolipoprotein E4 allele had a significant effect on LDL cholesterol response during the STAEST margarine only. Serum sitosterol and campesterol increased by 0.83 and 2.77 mg/l with the STEEST ($P < 0.001$), respectively and decreased by 1.18 and 2.60 mg/l with the STAEST margarine ($P < 0.001$). Increases of serum sitostanol and campestanol were 0.11 and 0.19 mg/l with the STAEST margarine ($P < 0.001$), respectively. No significant changes were found in serum fat-soluble vitamin and carotenoid concentrations when related to serum total cholesterol. Conclusions: STAEST and STEEST margarines reduced significantly and equally serum total and LDL cholesterol concentrations as part of a low-fat diet. Sponsorship: Grant to the University of Kuopio by Raisio Benecol Ltd, Raisio, Finland. European Journal of Clinical Nutrition (2000) 54, 715-725

Article classification: RCT

This is an example of a study in which all participants received the same interventions in a latin square design, and the participants were randomized to lines in the design. This study is eligible for inclusion in the Cochrane Library as an RCT.

AU: Johnson, B. A., Roache, J. D., Bordnick, P. S., and Ait-Daoud, N.

TI: Isradipine, a dihydropyridine-class calcium channel antagonist, attenuates some of d-methamphetamine's positive subjective effects: a preliminary study

SO: Psychopharmacology (Berl)

YR: 1999 June VL: 144 NO: 3 PG: 295-300

UI: 99361751

AB: RATIONALE: Dopamine (DA) pathways in the midbrain mediate d-methamphetamine's rewarding effects associated with its abuse liability. Isradipine, a dihydropyridine-class calcium channel antagonist, reduces the rewarding effects of psychostimulants such as cocaine and d-amphetamine, presumably by antagonizing these central DA pathways. This is the first experiment to test the hypothesis that the rewarding effects of d-methamphetamine, like other psychostimulants, can be reduced by isradipine. OBJECTIVE: We studied the effects of high dose isradipine (0.21 mg/kg orally), on the positive subjective effects associated with the abuse liability of low and high dose d-methamphetamine (0.21 mg/kg and 0.42 mg/kg orally, respectively). METHODS: Using a double-blind, double-dummy, placebo-controlled, Latin-Square,

cross-over design, 18 healthy male and female volunteers received each of the following six treatments separated by a rest period of 2-7 days: a) placebo+placebo; b) low-dose d-methamphetamine+placebo; c) high-dose d-methamphetamine+placebo; d) high dose isradipine+placebo; e) low-dose d-methamphetamine+high dose isradipine, and f) high-dose d-methamphetamine+high dose isradipine. RESULTS: d-Methamphetamine produced orderly increases in positive subjective measures of both stimulation and mood. Pre-treatment with isradipine significantly reduced some of these positive subjective effects and craving for d-methamphetamine. CONCLUSION: Isradipine as an anti-reward or craving reducing medication is a promising therapeutic agent for the treatment of d-methamphetamine dependence.

Article classification: CCT

This is an example of a study in which all the participants received the same treatments in a latin square design. A latin square design is a CCT design unless it specifically states that the subjects were randomized to a line in the square. This study is eligible for inclusion in the Cochrane Library as a CCT.

AU: Dimitriou, G., Greenough, A., and Laubscher, B.

TI: Appropriate positive end expiratory pressure level in surfactant-treated preterm infants

SO: Eur J Pediatr

YR: 1999 Nov. VL: 158 NO: 11 PG: 888-91

UI: 20009452

AB: Positive end expiratory pressure (PEEP) is routinely used when ventilating preterm infants, and high levels are recommended in those with severe respiratory distress syndrome (RDS). Elevation of PEEP increases lung volume, as does surfactant administration. We postulated that in surfactant-treated infants even modest PEEP levels could result in overdistension and (CO₂) retention. To test that hypothesis, lung volume, compliance and arterial blood gases were measured in eight preterm infants (median gestational age 28 weeks, range 26-35 weeks) at three PEEP levels. The infants, all with RDS, were studied at a median time of 18 h, (range 12-68 h) after their last dose of surfactant. Infants were routinely nursed at 3 cmH₂O of PEEP, the PEEP level was then raised to 6 cmH₂O or lowered to 0 cmH₂O in random order. The new setting was maintained for 20 min; the PEEP level was then changed to the third level (0 or 6 cmH₂O) again for 20 min. At the end of each 20-min period, lung volume, compliance and blood gases were measured. Lung volume was assessed by measuring functional residual capacity (FRC) using a helium dilution technique. Compliance was measured by relating the volume change from a positive pressure inflation maintained until no further volume change occurred to the pressure drop (peak inflating pressure PEEP). Increasing PEEP from 0 to 3 cmH₂O and particularly to 6 cmH₂O resulted in increases in FRC (P < 0.05), oxygenation (ns) and paCO₂ (P < 0.02). Specific compliance (compliance/FRC) (P < 0.05) and pH (P < 0.02) fell. CONCLUSION: Following surfactant treatment, relatively low levels of positive end expiratory pressure (<=3 cmH₂O) may be appropriate.

Article classification: RCT

This is an example of a study in which all participants receive the same treatments, and the order of treatments is random. The study is eligible for inclusion in the Cochrane Library.

AU: Fernandez, H., Pauthier, S., Sitbon, D., Vincent, Y., and Doumerc, S.

TI: [Role of conservative therapy and medical treatment in ectopic pregnancy: literature review and clinical trial comparing medical treatment and conservative laparoscopic treatment]

SO: Contracept Fertil Sex

YR: 1996 Apr. VL: 24 NO: 4 PG: 297-302

UI: 96254437

AB: OBJECTIVE: to compare methotrexate (MTX) to laparoscopic salpingotomy for conservative management of ectopic pregnancy (EP). DESIGN: prospective randomized study. PATIENTS: eighty-nine patients were randomized into 2 groups using a random number table. Inclusion criteria were an EP visualized by ultrasound with a pretherapeutic score ≤ 13 as assessed by 6 criteria graded from 1 to 3: gestational age, hCG level, P level, abdominal pain, volume of the hemoperitoneum, and diameter of the hematosalpinx. INTERVENTIONS: 1 mg/kg of MTX injected transvaginally into the ectopic pregnancy without anaesthesia or IM administration (1.5 mg/kg) when EP cannot be safely or easily punctured (group 1) versus laparoscopic salpingotomy (group 2). RESULTS: the success rates defined by hCG levels returned to normal (< 10 mIU/mL) were 43 out of 46 in group 1 and 40 out of 43 in group 2. Medical treatment was significantly associated with shorter post-operative stay (24 vs 46 hours). hCG return to normal was quicker after laparoscopic treatment (13 vs 29 days). Reproductive performances were similar in both groups. CONCLUSIONS: in selected cases of EP with a pretherapeutic score ≤ 13 , MTX treatment appeared to be as safe and efficient as was conservative treatment by laparoscopy, an expectant management should be offered as a treatment option only in women fulfilling the criteria for a good prognostic.

Article classification: RCT

This is an example of a study in which the method of randomization is explicitly laid out. It is eligible for inclusion in the Cochrane Library as an RCT.

AU: Ruutu, T., Volin, L., Parkkali, T., Juvonen, E., and Elonen, E.

TI: Cyclosporine, methotrexate, and methylprednisolone compared with cyclosporine and methotrexate for the prevention of graft-versus-host disease in bone marrow transplantation from HLA-identical sibling donor: a prospective randomized study

SO: Blood

YR: 2000 Oct. VL: 96 NO: 7 PG: 2391-2398

UI: 20458781

AB: The role of corticosteroids in the prophylaxis of graft-versus-host disease (GVHD) is not well established. We have conducted a prospective, randomized, open-label, single-center study about the effect of adding methylprednisolone (MP) to the widely used prophylactic regimen consisting of cyclosporine A and methotrexate. A total of 108 consecutive patients treated with allogeneic bone marrow transplantation from an HLA-

identical sibling donor for malignant blood disease were entered into the study; 53 patients were randomized to receive and 55 were randomized not to receive prophylactic MP. The dose of MP was 0.5 mg/kg on days 14 to 20, 1 mg/kg on days 21 to 34, 0.5 mg/kg on days 35 to 48, and thereafter the dose was slowly tapered and the administration discontinued on day 110. In the group given prophylactic MP, the incidence of acute GVHD was lower (19% vs 56%, $P = .0001$), there was a trend toward a lower incidence of chronic GVHD among low-risk patients ($P = .06$), and during the first 4 months the time spent at hospital was shorter and there were fewer infections. The total amount of MP given was similar in the study groups because of a higher incidence of acute GVHD and its treatment in the group of patients not given prophylactic MP. There were no significant differences between the study groups in relapse rate or survival. In conclusion, the addition of MP to the combination of cyclosporine and methotrexate markedly reduced the incidence of acute GVHD without causing untoward effects. The timing of corticosteroid administration is probably important for the efficacy. (Blood. 2000;96:2391-2398)

Article classification: RCT

This is an example of a study in which the method of randomization is not explicitly stated. We are not 100% certain that true statistical randomization was used, but we take the investigators at their word. When the study says randomization was used, the study is eligible for inclusion in the Cochrane Library as an RCT.

AU: Ronning, O. M. and Guldvog, B.

TI: Stroke unit versus general medical wards, II: neurological deficits and activities of daily living: a quasi-randomized controlled trial

SO: Stroke

YR: 1998 Mar. VL: 29 NO: 3 PG: 586-90

UI: 98165441

AB: BACKGROUND AND PURPOSE: The efficacy of stroke units has been extensively examined. It is unknown, however, whether the superiority of the stroke unit will remain after the increased focus on stroke treatment in general medicine. This study of patients admitted to the hospital early and with a short length of stay determines the effect and identifies certain important components of a stroke unit. METHODS: Five hundred fifty patients aged 60 years or older with acute stroke were allocated by a quasi-randomized design to a stroke unit or a general medical ward based on date of birth in the month. Patients admitted within 24 hours of onset were enrolled. Outcomes after 7 months were death, proportion needing long-term care, and change in neurological and functional state assessed by the Scandinavian Stroke Scale and Barthel Index.

RESULTS: Seven months after admission there was a trend in favor of the stroke unit in all outcome measures, but no significant differences in clinical outcomes were found except for change in the Scandinavian Stroke Scale score. Recurrent stroke during hospitalization occurred more often in the general medical ward ($P = .03$). The stroke unit was significantly more aggressive in mobilization out of bed ($P < .01$) and use of parenteral fluid ($P < .0001$), aspirin ($P < .0001$), antipyretics ($P < .0001$), and antibiotics ($P < .0001$). CONCLUSIONS: Our study confirms the benefit of the stroke unit, but the effects on the most reliable clinical outcomes were modest and insignificant. Treatment

in this stroke unit hastened recovery. More aggressive rehabilitation and use of parenteral fluid, aspirin, antipyretics, and antibiotics appeared in the stroke unit.

Article classification: CCT

This is an example of a study in which quasi-randomization was explicitly stated to have been used. The study is eligible for inclusion in the Cochrane Library as a CCT.

AU: Daoud, A. S., Batieha, A., Al-Sheyyab, M., Abuekteish, F., Obeidat, A., and Mahafza, T.

TI: Lack of effectiveness of dexamethasone in neonatal bacterial meningitis

SO: Eur J Pediatr

YR: 1999 Mar. VL: 158 NO: 3 PG: 230-3

UI: 99192268

AB: A clinical trial was conducted to determine whether dexamethasone as adjunctive therapy alters the outcome of bacterial meningitis in neonates. Fifty-two full-term neonates with bacterial meningitis were enrolled in a prospective study. Infants were alternately assigned to receive either dexamethasone or not. Twenty-seven received dexamethasone in addition to standard antibiotic treatment and 25 received antibiotics alone. Dexamethasone therapy was started 10-15 min before the first dose of antibiotics in a dose of 0.15 mg/kg per 6 h for 4 days. Baseline characteristics, clinical and laboratory features in the two groups were virtually similar. Both groups showed a similar clinical response and similar frequency of mortality and sequelae. Six (22%) babies in the treatment group died compared to 7 (28%) in the control group ($P = 0.87$). At follow up examinations up to the age of 2 years, 6 (30%) of dexamethasone recipients and 7 (39%) of the control group had mild or moderate/severe neurological sequelae. Audiological sequelae were seen in two neonates in the dexamethasone group compared to one in the control group. CONCLUSION: Adjunctive dexamethasone therapy does not improve the outcome of neonatal bacterial meningitis.

Article classification: CCT

This is an example of a study in which the method of allocation to treatment groups is quasi-random. Although the investigators do not use the terms "quasi-random" or "quasi-randomization", alternation is a method which is not statistically random but is intended to achieve the effect of randomization. Therefore, this study is eligible for inclusion in the Cochrane Library as a CCT.

AU: Kumar, S., Nixon, S. J., and MacIntyre, I. M.

TI: Laparoscopic or Lichtenstein repair for recurrent inguinal hernia: one unit's experience

SO: J R Coll Surg Edinb

YR: 1999 Oct. VL: 44 NO: 5 PG: 301-2

UI: 20018615

AB: Surgical treatment of recurrent inguinal hernia is controversial. This is a prospective study of 50 patients who had laparoscopic total extraperitoneal repair ($n = 25$) or Lichtenstein repair ($n = 25$) for recurrent inguinal hernia. The two groups of patients were comparable in age, sex and type of hernia. Post-operatively, a seroma or a wound

haematoma developed in 12 patients after Lichtenstein repair and in 4 patients after laparoscopic repair ($p < 0.05$). On average, analgesia was taken for 6.4 days after Lichtenstein repair compared with 3.4 days after laparoscopic repair ($p < 0.05$). In our unit, laparoscopic repair was associated with fewer complications and a significantly shorter duration of post-operative analgesia than Lichtenstein repair for recurrent inguinal hernia.

Article classification: CCT

This is an example of a study in which the participants were allocated to different treatments, but the investigators do not specify the method of allocation. When participants are prospectively allocated to different treatments by the investigators, and the method of allocation is uncertain, it is possible that randomization or quasi-randomization was used. The study is therefore eligible for inclusion in the Cochrane Library as a CCT.

AU: Holowaty, P., Feldman, L., Harvey, B., and Shortt, L.

TI: Cigarette smoking in multicultural, urban high school students

SO: J Adolesc Health

YR: 2000 Oct. VL: 27 NO: 4 PG: 281-288

UI: 20464973

AB: Purpose: To profile patterns of cigarette use among a multiethnic population of high school students, and identify important factors associated with cigarette use by ethnicity, in order to plan effective health promotion strategies. Methods: This cross-sectional study involved the completion of a lifestyle questionnaire by 1236 Grade 9-13 students (86% response rate) from 62 randomly selected classrooms in three urban high schools in Toronto. Chi-square analysis of the association between tobacco use and other variables took account of the clustered sample using CSAMPLE in Epi Info. Results: The students self-identified their ethnicity as follows: 388 Canadian, 269 European, 171 East Indian, 137 Asian, 76 West Indian, and 194 "other." Students who identified themselves as Canadians were significantly more likely to be current smokers (29%) than students reporting other ethnicities (13%). There was no apparent increase in smoking rates for immigrants after 2 or more years in Canada. Current drinking, sexual activity, and especially friends smoking was most strongly associated with current smoking for most ethnic groups, although the relative importance of these variables was not identical for all groups. Conclusions: Prevention programs may benefit from a focus on the influence of peer smoking and on the grouping together of lifestyle factors associated with smoking for students in all ethnic groups in this multicultural city.

Article classification: N/A

This is an example of a study in which the phrase "randomly selected" is used. The participants were randomly selected to participate in the study, but they were not randomly allocated to different interventions. In fact, this is a cross-sectional study, and no interventions took place. Studies in which participants were randomly selected to participate but were not randomly allocated to different interventions are not eligible for inclusion in the Cochrane Library.

AU: Jonas, J. B. and Budde, W. M.

TI: Loosening of single versus double running sutures in penetrating keratoplasty for keratoconus

SO: Graefes Arch Clin Exp Ophthalmol

YR: 1999 June VL: 237 NO: 6 PG: 522-3

UI: 99306284

AB: PURPOSE: Purpose of the study was to evaluate single versus double running sutures in penetrating keratoplasty for keratoconus with respect to suture loosening.

METHODS: Eighty-eight patients were consecutively operated for keratoconus by the same surgeon with the same surgical technique. For the first 45 patients, a single running 10-0 nylon suture was used. For the remaining 43 patients, double running 10-0 nylon sutures were taken. RESULTS: Suture loosening was observed significantly ($P < 0.001$; Chi-Square test) more often in the patients with a single running suture (12/45=27%) than in the patients with double running sutures (0/43=0%).

CONCLUSIONS: The results indicate that double running sutures in comparison to a single running suture may be helpful in preventing suture loosening in penetrating keratoplasty for keratoconus.

Article classification: N/A

This is an example of a study in which participants were allocated to treatment groups using a method which we know to be neither randomization nor quasi-randomization.

The study is not eligible for inclusion in the Cochrane Library.

AU: Jauss, M., Krieger, D., Hornig, C., Schramm, J., and Busse, O.

TI: Surgical and medical management of patients with massive cerebellar infarctions: results of the German-Austrian Cerebellar Infarction Study

SO: J Neurol

YR: 1999 Apr. VL: 246 NO: 4 PG: 257-64

UI: 99294113

AB: Surgical intervention (ventricular drainage or decompressive craniotomy) may be necessary in patients with cerebellar infarction if mass effect develops. However, patient selection and timing of surgery remain controversial, and there are few data on clinical signs in the early course that are predictive for outcome. The clinical course and neuroradiological features of 84 patients (aged 22-78, mean 58.5 years) with massive cerebellar infarction confirmed by computed tomography were prospectively observed for 21 days after admission and at 3-month follow-up using a standardized protocol. Data were gathered from 1992 to 1996 in 17 centers. The patients were assigned to three treatment groups depending on the decision of the primary caretaker: 34 underwent craniotomy and evacuation, 14 received ventriculostomy, and 36 were treated medically. Treatment groups differed regarding the level of consciousness, signs of mass effect in computed tomography and signs of brainstem involvement. The overall risk for poor outcome depended on the level of consciousness after clinical deterioration (odds ratio = 2.8). Subgroup analysis of awake/drowsy or somnolent/stupor patients revealed no relationship to treatment. The vascular territory involved did not affect outcome. Surgical treatment for massive cerebellar infarctions was not found to be superior to medical treatment in awake/drowsy or somnolent/stupor patients. Half of all

patients deteriorating to coma treated with ventricular drainage or decompressive craniotomy had a meaningful recovery. We were unable to compare surgical versus medical therapy in this subgroup due to lack of control group. This study supports the notion that the level of consciousness is the most powerful predictor of outcome, superior to any other clinical sign and treatment assignment. Deterioration of consciousness typically occurred between days 2 and 4, with a maximum on day 3.

Article classification: N/A

This is an example of a study in which participants were allocated to treatments depending on the clinical judgement of their physicians. This is clearly not a random or quasi-random method of allocation and the study is therefore not eligible for inclusion in the Cochrane Library.

AU: Eltabbakh, G. H., Piver, M. S., Hempling, R. E., Recio, F. O., and Blumenson, L. E.
TI: Prolonged disease-free survival by maintenance chemotherapy among patients with recurrent platinum-sensitive ovarian cancer

SO: Gynecol Oncol

YR: 1998 Nov. VL: 71 NO: 2 PG: 190-5

UI: 99045523

AB: OBJECTIVE: The aim of this study was to determine the potential benefit and complications of prolonged salvage and maintenance chemotherapy among patients with recurrent epithelial ovarian cancer who achieve response to salvage chemotherapy. METHODS: Patients with recurrent platinum-sensitive epithelial ovarian cancer who were treated between 1982 and 1996 and achieved complete response to platinum-based salvage chemotherapy were offered prolonged (1 year) monthly salvage followed by maintenance (every 8 weeks) chemotherapy. Patients who accepted such treatment (n = 16) were compared to those who refused and discontinued therapy (n = 11) with regard to overall survival from time of initial diagnosis and overall and disease-free survival from time of recurrence. Chemotherapy-related toxicity in the study group was recorded. Survival curves were constructed according to the Kaplan and Meier method and survival curves were compared using the log-rank test. RESULTS: Patients in the study and control groups were similar with regard to age, stage, histology, grade, performance status, primary cytoreductive surgery, type of primary and salvage chemotherapy, and method of assessment of tumor response. The study group had a significantly longer disease-free interval from date of recurrence than the control group (median: 35.0 versus 6.0 months, respectively, P = 0.001). The study group had longer overall survival from date of recurrence than the control group. However, the difference did not achieve statistical significance (median: 119 versus 90 months, respectively, P = 0.056). There was no significant difference between the study group and the control group as to survival from date of initial diagnosis (median: 157 versus 124 months, respectively, P = 0.28). Chemotherapy-related toxicity was minimal. CONCLUSIONS: Prolonged salvage and maintenance chemotherapy is a safe method of treatment that may extend disease-free interval among patients with platinum-sensitive recurrent epithelial ovarian cancer who achieve response to salvage chemotherapy. These preliminary results need to be confirmed by a larger prospective randomized trial. Copyright 1998 Academic Press.

Article classification: N/A

This is an example of a study in which the participants selected their own treatments. This is clearly not a random or quasi-random method of allocation, and therefore this study is not eligible for inclusion in the Cochrane Library.

AU: Hadigan, C., Miller, K., Corcoran, C., Anderson, E., Basgoz, N., and Grinspoon, S.

TI: Fasting hyperinsulinemia and changes in regional body composition in human immunodeficiency virus-infected women

SO: J Clin Endocrinol Metab

YR: 1999 June VL: 84 NO: 6 PG: 1932-7

UI: 99299904

AB: A novel lipodystrophy syndrome (characterized by insulin resistance, hypertriglyceridemia, and fat redistribution) has recently been described in human immunodeficiency virus (HIV)-infected patients. However, investigation of the lipodystrophy syndrome has generally been limited to men; and a comprehensive evaluation of insulin, lipids, and regional body composition has not been performed in the expanding population of HIV-infected women. In this study, we assessed fasting insulin, lipid levels, virologic parameters, and regional body composition, using dual-energy x-ray absorptiometry, in a cohort of 75 HIV-infected women (age, 25-46 yr), in comparison with 30 healthy weight-matched premenopausal control subjects. HIV-infected women demonstrated significant truncal adiposity (38.5 +/- 0.9 vs. 34.9 +/- 1.3%, $P < 0.05$) hyperinsulinemia (15.9 +/- 1.5 vs. 7.5 +/- 0.6 microU/mL, $P < 0.001$) and an increased insulin-to-glucose ratio (0.2 +/- 0.02 vs. 0.1 +/- 0.03, $P < 0.001$), compared with control subjects. Insulin and the insulin-to-glucose ratio were increased, even among HIV-infected patients with low body weight (<90% of ideal body weight) (insulin, 13.3 +/- 2.8 microU/mL, $P < 0.01$ vs. control; insulin/glucose, 0.2 +/- 0.04, $P < 0.01$ vs. control). Insulin and the insulin-to-glucose ratio were most significantly elevated among patients with increased truncal adiposity (insulin, 28.2 +/- 3.2 microU/mL, $P < 0.001$ vs. control; insulin/ glucose, 0.32 +/- 0.04, $P < 0.001$ vs. control). In contrast, no differences in insulin were seen in relation to protease inhibitor (PI) use. Similarly, HIV-infected women also demonstrated significant hypertriglyceridemia (144 +/- 15 vs. 66 +/- 23 mg/dL, $P < 0.01$ vs. controls), which was present even among low-weight patients (148 +/- 32 mg/dL, $P < 0.001$ vs. control) but was not related to truncal adiposity or PI usage. These data demonstrate significant hyperinsulinemia and truncal adiposity in HIV-infected women. Our data suggest that these metabolic abnormalities occur at baseline in HIV-infected women, independent of PI use. However, these data do not rule out a direct effect of PI therapy on fat metabolism or indirect effects of PI therapy to further worsen glucose and lipid homeostasis in association with weight gain and disease recovery.

Article classification: N/A

This is an example of a study in which the participants are divided into two groups defined by some pre-existing characteristic of the participants. Here the two groups consist of HIV-infected women and healthy women. The purpose of this study is to

compare the results of a single intervention in two different types of participants, and there is no comparison between interventions. The study is not eligible for inclusion in the Cochrane Library.

AU: Brutsche, M. H., Brutsche, I. C., Munawar, M., Langley, S. J., Masterson, C. M., Daley-Yates, P. T., Brown, R., Custovic, A., and Woodcock, A.

TI: Comparison of pharmacokinetics and systemic effects of inhaled fluticasone propionate in patients with asthma and healthy volunteers: a randomised crossover study

SO: Lancet

YR: 2000 Aug. VL: 356 NO: 9229 PG: 556-61

UI: 20405166

AB: BACKGROUND: Inhaled corticosteroids are currently the cornerstone of asthma treatment. Some studies of high-dose fluticasone propionate in patients with no or mild asthma have, however, suggested substantial systemic absorption. We investigated the pharmacokinetics of fluticasone propionate in patients with asthma receiving appropriate doses for severity. METHODS: We did a double-blind, randomised, crossover study in 11 patients with asthma and 13 matched healthy controls (age 20-65 years; asthma patients forced expiratory volume in 1 s <75% and stable on high-dose inhaled corticosteroids). Patients received one 1000 microg intravenous dose or 1000 microg daily for 7 days inhaled (via spacer device) fluticasone propionate. In the 12 h after dosing, we monitored plasma fluticasone propionate and cortisol concentrations by mass spectrometry and competitive immunoassay with use of direct chemiluminescence. Analysis was by intention to treat. FINDINGS: After inhalation, geometric mean values were significantly lower in the asthma group than in controls for fluticasone propionate plasma area under curve (1082 [95% CI 850-1451] vs 2815 pg mL⁻¹ h⁻¹ [2262-3949], -62% difference [45-72]; p<0.001), maximum concentrations (117 [91-159] vs 383 pg/mL [302-546], -68% [-50 to -81]; p<0.001), and systemic bioavailability (10.1 [7.9-14.0] vs 21.4% [15.4-32.2], -54% [-27 to -70]; p=0.001). Intravenous-dose clearance, volume of distribution at steady state, plasma half-life, and mean residence time, were similar in the two groups. Less suppression of plasma cortisol concentrations was seen in the asthma group than in controls 4-12 h after inhaled fluticasone propionate. INTERPRETATION: Systemic availability of fluticasone propionate is substantially less in patients with moderate to severe asthma than in healthy controls. Inhaled corticosteroids that are absorbed through the lungs need to be assessed in patients who are receiving doses appropriate for disease severity, and not in normal volunteers.

Article classification: RCT

This is an example of a study in which different types of participants are compared (here they are asthmatics and healthy persons) but both types of participants receive both interventions in a randomized fashion. The purpose of this study is compare the results of two intervention within and between the different groups of participants. This study is eligible for inclusion in the Cochrane Library.

AU: Shushan, A., Mohamed, H., and Magos, A. L.

TI: A case-control study to compare the variability of operating time in laparoscopic and open surgery

SO: Hum Reprod

YR: 1999 June VL: 14 NO: 6 PG: 1467-9

UI: 99287964

AB: The purpose of this study was to compare the variability of operating times for some of the most common gynaecological procedures performed laparoscopically and by open surgery. The case notes of 60 women randomly selected from a cohort of 600 who had undergone laparoscopic surgery for ectopic pregnancy, ovarian cysts, leiomyoma and hysterectomy were reviewed. These patients were matched with an equal number of women who had been treated by open surgery for similar indications. Additional matching criteria included age (+/-2 years), size of the lesion in cases of ovarian cysts and fibroids (+/-3 cm), the period of amenorrhoea in ectopic pregnancies, and uterine size and pelvic pathology in women undergoing hysterectomy. Comparison of laparoscopy and laparotomy showed that the mean procedure times were similar for the two routes of surgery, with the exception of hysterectomy which took significantly longer if done laparoscopically. The duration of laparoscopic surgery for ectopic pregnancy, ovarian cystectomy and hysterectomy was significantly less predictable than at laparotomy. These data indicate that with the exception of hysterectomy, the average operating time for laparoscopic procedures is comparable to that for laparotomy. In contrast, the variability of duration of laparoscopic surgery tends to be much greater than with laparotomy for all procedures considered.

Article classification: N/A

This is an example of a study in which the participants are compared to non-participants matched on age and other factors. The participants were given the treatment being investigated, then compared to non-participants, chosen after the intervention had been completed, who were not given the treatment. Because participants were not randomly allocated to treatments, and because the persons not given the treatment were selected retrospectively, this study is not eligible for inclusion in the Cochrane Library.

AU: Bowman, R. J., Soma, O. S., Alexander, N., Milligan, P., Rowley, J., Faal, H., Foster, A., Bailey, R. L., and Johnson, G. J.

TI: Should trichiasis surgery be offered in the village? A community randomised trial of village vs. health centre-based surgery

SO: Trop Med Int Health

YR: 2000 Aug. VL: 5 NO: 8 PG: 528-33

UI: 20448559

AB: INTRODUCTION: Surgery for trachomatous trichiasis prevents blindness and is advocated by the WHO as part of the SAFE strategy for the global elimination of trachoma. We conducted a randomised community trial to investigate the effect of providing surgery in villages on surgical uptake in The Gambia. METHODS: 56 villages from two divisions were assigned to eight pairs of clusters matched by geographical division and proximity. One cluster from each pair was randomly assigned to receive village-based surgery and the other cluster health centre-based surgery. Outcome measures were uptake rates and surgical results after 1 week and 3 months. The paired

t-test was used to analyse the results. RESULTS: Overall uptake was 66% in the village-based clusters and 44% in the health centre-based clusters. Subjects in the village-based surgery arm had significantly shorter journey times ($P = 0.01$) and lower costs ($P = 0.002$). The mean difference in absolute acceptance rates of surgery was 20% better in village-based clusters (95% CI -9 to + 49%, $P = 0.15$), which would equate to an improvement of 45% (95% CI -20% to 120%) on the average acceptance rates of 44% in the health centre-based group. CONCLUSION: These results strongly suggest better surgical uptake when surgery is provided in patients' villages due to lower cost to the patient, time saved and less fear of the operation.

Article classification: RCT

This is an example of a study which used matching on the participants and then randomized the participants within the matched groups to receive different treatments. This study is eligible for inclusion in the Cochrane Library.

AU: Lallemand, M., Jourdain, G., Le Coeur, S., Kim, S., Koetsawang, S., Comeau, A. M., Phoolcharoen, W., Essex, M., McIntosh, K., and Vithayasai, V.

TI: A trial of shortened zidovudine regimens to prevent mother-to-child transmission of human immunodeficiency virus type 1. Perinatal HIV Prevention Trial (Thailand)

Investigators

SO: N Engl J Med

YR: 2000 Oct. VL: 343 NO: 14 PG: 982-91

UI: 20452482

AB: BACKGROUND: The optimal duration of zidovudine administration to prevent perinatal transmission of human immunodeficiency virus type 1 (HIV-1) should be determined to facilitate its use in areas where resources are limited. METHODS: We conducted a randomized, double-blind equivalence trial of zidovudine starting in the mother at 28 weeks' gestation, with 6 weeks of treatment in the infant (the long-long regimen), which is similar to protocol 076; zidovudine starting at 35 weeks' gestation, with 3 days of treatment in the infant (the short-short regimen); a long-short regimen; and a short-long regimen. The mothers received zidovudine orally during labor. The infants were fed formula and were tested for HIV DNA at 1, 45, 120, and 180 days. After the first interim analysis, the short-short regimen was stopped. RESULTS: A total of 1437 women were enrolled. At the first interim analysis, the rates of HIV transmission were 4.1 percent for the long-long regimen and 10.5 percent for the short-short regimen ($P=0.004$). For the entire study period, the transmission rates were 6.5 percent (95 percent confidence interval, 4.1 to 8.9 percent) for the long-long regimen, 4.7 percent (95 percent confidence interval, 2.4 to 7.0 percent) for the long-short regimen, and 8.6 percent (95 percent confidence interval, 5.6 to 11.6 percent) for the short-long regimen. The rate of in utero transmission was significantly higher with the two regimens with shorter maternal treatment (5.1 percent) than with the two with longer maternal treatment (1.6 percent). CONCLUSIONS: The short-short zidovudine regimen is inferior to the long-long regimen and leads to a higher rate of perinatal HIV transmission. The long-short, short-long, and long-long regimens had equivalent efficacy. However, the higher rate of in utero transmission with the short-long regimen suggests that longer treatment of the infant cannot substitute for longer treatment of the mother.

Article classification: RCT

AU: Yang, B., Zhang, B., and Tang, Z.

TI: [Screening and early diagnosis of primary liver cancer]

SO: Chung Hua Kan Tsang Ping Tsa Chih

YR: 1999 Sept. VL: 7 NO: 3 PG: 130-1

UI: 20038969

AB: OBJECTIVE: To investigate the value of screening for early diagnosis of primary liver cancer (PLC). METHODS: A total of 18,816 persons, who were high-risk population of PLC, were divided randomly to allocated screening group and control group. In the screening group every individual was checked up by serum AFP test and ultrasound every 6 months but those in the control group were not. RESULTS: Eighty-six patients with PLC were detected in the screening group, while 51 patients with PLC occurred in the control group. In patients from the screening group 60.5% were in the early stage, 45.3% of them were with small liver cancer. However, in the control group the figures were 0 and 0 respectively. In the screening group, 57 patients with PLC were detected by follow-up screening every 6 months, 77.2% patients of this series were in the early stage. However in the screening group the other 29 patients with PLC were detected by screening but they were not followed up every 6 months. Early-stage patients were only 27.6% in this series. CONCLUSION: This suggests mass screening, especially continual screening every 6 months in fixed population can diagnose PLC early.

Article classification: RCT

AU: Dieterle, T., Battagay, E., Bucheli, B., and Martina, B.

TI: Accuracy and 'range of uncertainty' of oscillometric blood pressure monitors around the upper arm and the wrist

SO: Blood Press Monit

YR: 1998 VL: 3 NO: 6 PG: 339-46

UI: 99272801

AB: BACKGROUND: Although they have been marketed widely, few data about the diagnostic accuracy of blood pressure monitors are available. METHODS: Repeated measurements of blood pressures in 85 patients were performed in random sequence with two oscillometric blood pressure monitors around the upper arm (Visomat OZ2) and the wrist (Omron R3) and with a standard sphygmomanometer. The oscillometric blood pressure monitors were validated according to protocols of the British Hypertension Society (BHS) and the American Association for the Advancement of Medical Instrumentation (AAMI). Subsequently, sensitivity and specificity of these monitors for the diagnosis of hypertension or exclusion of the possibility of its presence in a general medical outpatient population were calculated. RESULTS: Sphygmomanometric readings exceeded oscillometric blood pressure measurements by 3.7+/-7.5/4.8+/-5.6 mmHg (systolic/diastolic) for the upper arm and 5.7+/-6.2/6.8+/-6.8 mmHg for the wrist. Deviations occurred in both directions and were higher for blood pressures in the hypertensive range. Oscillometric blood pressure measurements at the upper arm, but not at the wrist, satisfied validation criteria of BHS and AAMI protocols. Optimal sensitivity and specificity for the diagnosis of hypertension, defined as blood

pressure > 140/90 mmHg with a standard sphygmomanometer, was achieved with blood pressure limits of 133/82 mmHg for the Visomat OZ and 131/80 mmHg for the Omron R3. CONCLUSIONS: Average sphygmomanometer values exceed oscillometrically measured blood pressure values but individual disagreements cannot be predicted. Measurements at the upper arm are more accurate than are those at the wrist according to the validation protocols of the BHS and AAMI. Additional appraisal of sensitivities and specificities and of a 'range of uncertainty' for the diagnosis of hypertension may allow better judgement of accuracy of individual oscillometric blood pressure measurements.

Article classification: RCT

AU: Krown, S. E., Burk, M. W., Kirkwood, J. M., Kerr, D., Morton, D. L., and Oettgen, H. F.

TI: Human leukocyte (alpha) interferon in metastatic malignant melanoma: the American Cancer Society phase II trial

SO: Cancer Treat Rep

YR: 1984 May VL: 68 NO: 5 PG: 723-6

UI: 84205507

AB: Forty-four evaluable patients with metastatic malignant melanoma confined to the skin, subcutaneous tissues, lymph nodes, and/or lung were randomly assigned to receive either 1 X 10⁶, 3 X 10⁶, or 9 X 10⁶ units of partially purified human leukocyte (alpha) interferon by daily im injection for 42 days. One patient achieved a partial response, two had minor responses, and three others had mixed responses. The only partial response was observed at the lowest dose of interferon. Toxicity increased in frequency and intensity with increasing interferon dose. This preparation of interferon at the doses, route, and schedule used appears to have little efficacy in metastatic malignant melanoma.

Article classification: RCT

AU: Duse, M., Merlini, R., Gardenghi, R., and Porter, V.

TI: [Oxatomide in the treatment of atopic dermatitis]

SO: Minerva Pediatr

YR: 1998 July-1998 Aug. VL: 50 NO: 7-8 PG: 359-65

UI: 99139206

AB: BACKGROUND: This study evaluated the efficacy and tolerability of oxatomide in patients with atopic dermatitis, caused by alimentary allergy established by prick test and/or Rast and/or challenge test. METHODS: In the study, carried out in a paediatric clinic, 40 children (24 males, 16 females), aged between 6 months and 12 years, were randomized in two groups. Twenty children were treated with oxatomide (1 mg/kg/day) in one evening dose and the other 20 were treated at the same dosage, divided into two administrations. In the case of poor therapeutic response, 15 days after the start of treatment, it was possible to double the dosage. The skin symptoms were monitored for the efficacy. RESULTS: For all symptoms there was a significant reduction of severity within the fifteenth day ($p < 0.01$). Twenty eight children showed significant improvement with the disappearance of both cutaneous lesions and itching; to achieve these results in four cases (3 BID, 1 UID) it was necessary to double the dose (2

mg/kg/day). Eight children achieved a fair control of itching, with a slight improvement of eczema, while five children, despite the increase in dosage of the drug, did not get any substantial benefit. Three children were lost in follow-up, while in another case treatment was suspended because of the onset of an urticarious rash. CONCLUSIONS: The results confirm the efficacy of oxatomide in the control of itching connected with alimentary allergy independently of the posological scheme. Tolerability was excellent in both groups and no important side-effects were recorded.

Article classification: RCT

AU: Barbey, J. T., Sale, M. E., Woosley, R. L., Shi, J., Melikian, A. P., and Hinderling, P. H.

TI: Pharmacokinetic, pharmacodynamic, and safety evaluation of an accelerated dose titration regimen of sotalol in healthy middle-aged subjects

SO: Clin Pharmacol Ther

YR: 1999 July VL: 66NO: 1 PG: 91-9

UI: 99357183

AB: BACKGROUND: Current labeling recommends that therapy with sotalol be initiated in a monitored setting at 80 mg every 12 hours for 2 to 3 days, followed by 120 to 160 mg every 12 hours for at least 2 days before safety and efficacy can be ascertained and patients discharged. An accelerated titration regimen that shortens hospital stay without compromising patient safety would improve the usefulness of the drug. Although such regimens have been used by clinicians, they have not been formally evaluated.

METHODS: Healthy, middle-aged sedentary men and women received sotalol in a double-blind, two-way crossover study with a 2-week washout phase to evaluate an accelerated titration regimen--placebo every 6 hours for four doses, followed by 80 mg sotalol every 6 hours for four doses, then 160 mg sotalol every 12 hours for nine doses--and compare it with the standard titration--placebo alternating with 80 mg sotalol every 6 hours for eight doses, followed by 160 mg sotalol every 12 hours for nine doses. QT intervals, RR intervals, and sotalol concentrations in plasma were measured at specific times throughout the study and during washout in a similar fashion for both regimens.

RESULTS: Thirty-four subjects completed both regimens. The target prolongation of QTc (90% of the value achieved at steady state) was achieved 22 1/2 hours sooner with the accelerated titration regimen (P = .0003). There were no cardiovascular adverse events during either loading phase. At no time during the accelerated titration regimen did the sotalol concentrations in plasma or the QTc or RR interval prolongation exceed the values eventually achieved at steady state. The relationship between sotalol concentration and QTc was linear and independent of the regimen. CONCLUSION: The accelerated titration regimen for sotalol can shorten the time to attain the dosage usually required to effectively control arrhythmias, without excessive QT prolongation and the associated increased risk of torsades de pointes. The hospital stay of patients in whom antiarrhythmic therapy with sotalol is initiated can be shortened by 1 day if this accelerated titration regimen is used.

Article classification: CCT

AU: Bozorgzadeh, A., Pizzi, W. F., Barie, P. S., Khaneja, S. C., LaMaute, H. R., Mandava, N., Richards, N., and Noorollah, H.

TI: The duration of antibiotic administration in penetrating abdominal trauma

SO: Am J Surg

YR: 1999 Feb. VL: 177 NO: 2 PG: 125-31

UI: 99219248

AB: BACKGROUND: The epidemiology of penetrating abdominal trauma is changing to reflect an increasing incidence of multiple injuries. Not only do multiple injuries increase the risk of infection, a very high risk of serious infection is conferred by immunosuppression from hemorrhage and transfusion and the high likelihood of intestinal injury, especially to the colon. Optimal timing and choice of presumptive antibiotic therapy has been established for penetrating trauma, but duration has not been studied extensively in such seriously injured patients. The purpose of this study was to test the hypothesis that 24 hours of antibiotic therapy remains sufficient to reduce the incidence of infection in penetrating abdominal trauma. METHODS: Three hundred fourteen consecutive patients with penetrating abdominal trauma were prospectively randomized into two groups: Group I received 24 hours of intravenous cefoxitin (1 g q6h) and group II received 5 days of intravenous cefoxitin. The development of a deep surgical site (intra-abdominal) infection as well as any type of nosocomial infection, as defined by the Centers for Disease Control and Prevention, (ie, surgical site infections, catheter-related infections, urinary tract, pneumonia), was recorded. Hospital length of stay was a secondary endpoint. Statistical analysis included chi-square tests for coordinate variables and two-tailed unpaired t tests for continuous variables. The independence of risk factors for the development of infection was assessed by multivariate analysis of variance. Significance was determined when $P < 0.05$. RESULTS: Three hundred patients were evaluable. There was no postoperative mortality, and no differences in overall length of hospitalization between groups. The duration of antibiotic treatment had no influence on the development of any infection ($P = 0.136$) or an intraabdominal infection ($P = 0.336$). Only colon injury was an independent predictor of the development of an intraabdominal infection ($P = 0.0031$). However, the overall infection incidence was affected by preoperative shock ($P = 0.003$), colon ($P = 0.0004$), central nervous system (CNS) injuries ($P = 0.031$), and the number of injured organs ($P = 0.026$). Several factors, including intraoperative shock ($P = 0.021$) and injuries to the colon ($P = 0.0008$), CNS ($P = 0.0001$), and chest ($P = 0.0006$), were independent contributors to prolongation of the hospital stay. CONCLUSIONS: Twenty-four hours of presumptive intravenous cefoxitin versus 5 days of therapy made no difference in the prevention of postoperative infection or length of hospitalization. Infection was associated with shock on admission to the emergency department, the number of intra-abdominal organs injured, colon injury specifically, and injury to the central nervous system. Intra-abdominal infection was predicted only by colon injury. Prolonged hospitalization was associated with intraoperative shock and injuries to the chest, colon, or central nervous system.

Article classification: RCT

AU: Newton, R. U., Kraemer, W. J., and Hakkinen, K.

TI: Effects of ballistic training on preseason preparation of elite volleyball players

SO: Med Sci Sports Exerc

YR: 1999 Feb. VL: 31 NO: 2 PG: 323-30

UI: 99161586

AB: PURPOSE: The purpose of this study was to determine whether ballistic resistance training would increase the vertical jump (VJ) performance of already highly trained jump athletes. METHODS: Sixteen male volleyball players from a NCAA Division I team participated in the study. A Vertec was used to measure standing vertical jump and reach (SJR) and jump and reach from a three-step approach (AJR). Several types of vertical jump tests were also performed on a Plyometric Power System and a forceplate to measure force, velocity, and power production during vertical jumping. The subjects completed the tests and were then randomly divided into two groups, control and treatment. All subjects completed the usual preseason volleyball on-court training combined with a resistance training program. In addition, the treatment group completed 8 wk of squat jump training while the control group completed squat and leg press exercises at a 6RM load. Both groups were retested at the completion of the training period. RESULTS: The treatment group produced a significant increase in both SJR and AJR of 5.9+/-3.1% and 6.3+/-5.1%, respectively. These increases were significantly greater than the pre- to postchanges produced by the control group, which were not significant for either jump. Analysis of the data from the various other jump tests suggested increased overall force output during jumping, and in particular increased rate of force development were the main contributors to the increased jump height. CONCLUSIONS: These results lend support to the effectiveness of ballistic resistance training for improving vertical jump performance in elite jump athletes.

Article classification: RCT

AU: Irigoyen, M. M., Kurth, R. J., and Schmidt, H. J.

TI: Learning primary care in medical school: does specialty or geographic location of the teaching site make a difference?

SO: Am J Med

YR: 1999 May VL: 106 NO: 5 PG: 561-4

UI: 99266760

AB: PURPOSE: The Liaison Committee on Medical Education mandates a core curriculum in primary care but does not specify its content or structure. In this study, we explored the question of whether primary care specialty or geographic location affects student learning and satisfaction. METHODS: From 1994 to 1996, 294 third-year medical students at one medical school in New York state were randomly assigned to multiple teaching sites for a required 5-week primary care clerkship. Independent predictor variables were primary care specialty of the preceptor (family medicine, medicine, pediatrics, or joint medicine and pediatrics) and geographic location of the site (urban, suburban, rural). Outcome measures included four areas of student satisfaction, one of patient volume, and two of student performance. RESULTS: Primary care specialty had no detectable association with the outcome measures, except for a lower rating of patient diversity in pediatric experiences ($P < 0.001$). Geographic location of the site had a significant association with all measures of student satisfaction and patient volume (all P values < 0.001). Students at rural sites rated the experience more highly and saw on average 15 more patients per rotation. Ratings of student satisfaction remained high after adjusting for patient volume. Primary care specialty and geographic location did not influence student performance in the clerkship or scores on

standardized patient examination. CONCLUSIONS: Rural geographic location of teaching site, but not primary care specialty, was associated with higher student satisfaction. However, higher student satisfaction ratings did not correspond to better student performance. Provided that all sites meet the screening criteria for inclusion in a teaching program, these findings support the continued development of high-quality, heterogeneous, interdisciplinary, primary care experiences.

Article classification: RCT

AU: Peters, T., Somerset, M., Baxter, K., and Wilkinson, C.

TI: Anxiety among women with mild dyskaryosis: a randomized trial of an educational intervention

SO: Br J Gen Pract

YR: 1999 May VL: 49 NO: 442 PG: 348-52

UI: 20201122

AB: BACKGROUND: Women with mild dyskaryosis are currently managed by six-month cytological surveillance. While there is good evidence that women suffer psychological distress on receipt of an abnormal test, and that this is amenable to educational intervention, it remains uncertain whether this distress is prolonged and, if so, how it should best be managed. AIM: To investigate whether a structured educational intervention containing a risk communication package impacts upon psychological sequelae associated with this surveillance. METHOD: A pragmatic cluster-randomized controlled trial during 14 months in 1995 and 1996, based in general practices in Avon and South Glamorgan, that compared the intervention with standard care. Follow-up was by postal questionnaire at six weeks and four months after the screening laboratory had reported the test result. The intervention was an invitation to attend the general practice to consult with a practice nurse trained to deliver the package. The main outcome measures were Spielberger state-anxiety, SF-36 Mental Health dimension, four condition-specific questions regarding concerns about gynaecological health and timing of the repeat smear test, and attendance for the repeat test. RESULTS: Of 514 eligible women, 270 were recruited, of whom 240 returned the six-week questionnaire and 181 returned the four-month questionnaire. On all but one outcome measure, the differences between the groups were not statistically significant. At six-week follow-up, the proportion who preferred the repeat test to be sooner than six months was statistically significantly higher among controls (74% versus 53%; 95% CI = 9% to 33%). At the four-month follow-up, the difference was 7% (95% CI = -7% to 21%). CONCLUSION: There appear to be high levels of anxiety during surveillance for mild dyskaryosis that were not reduced by the intervention. Given that a personally delivered educational intervention designed to reduce anxiety could be viewed as the best available practice, it is of concern that women in the intervention group demonstrated sustained anxiety over a four-month period. The research agenda therefore seems to return to the fundamental question of whether surveillance should be the management of choice.

Article classification: RCT

AU: O'Donnell, M., Parker, G., Proberts, M., Matthews, R., Fisher, D., Johnson, B., and Hadzi-Pavlovic, D.

TI: A study of client-focused case management and consumer advocacy: the Community and Consumer Service Project

SO: Aust N Z J Psychiatry

YR: 1999 Oct. VL: 33NO: 5 PG: 684-93

UI: 20011076

AB: OBJECTIVE: The study investigated the provision of client-focused services to community-based clients with schizophrenia and bipolar disorder. It hypothesised that the delivery of more client-focused services would improve client outcome in terms of functioning, disability and satisfaction with services. Client-focused services were developed using an empowerment model of case management and by the addition of consumer advocates. METHOD: Clients referred for case management were randomly allocated to one of three groups: standard case management (n = 35), client-focused case management (n = 39), or client-focused case management plus consumer advocacy (n = 45). Measures of functioning, disability, quality of life, burden of care and service satisfaction were measured at baseline and 12 months. Outcome data were collected concerning number and duration of hospital readmission, crisis intervention and compliance with treatment and services. RESULTS: While there were no differences between the groups on quantitative measures of functioning, disability, quality of life, service satisfaction and burden of care, there were significant between-group differences on qualitative measures of satisfaction with services. CONCLUSIONS: Several methodological difficulties hampered interpretation of the findings. Although clients did not differ on outcome measures of functioning and disability, the group receiving client-focused case management reported greater satisfaction with service delivery.

Article classification: RCT

AU: Aziz, I. and Lipworth, B. J.

TI: In vivo effect of albuterol on methacholine-contracted bronchi in conjunction with salmeterol and formoterol

SO: J Allergy Clin Immunol

YR: 1999 May VL: 103 NO: 5 Pt 1 PG: 816-22

UI: 99262549

AB: BACKGROUND: It has been shown in vitro that prior treatment with salmeterol and formoterol antagonizes the relaxant effect of albuterol in carbachol-contracted human bronchi. OBJECTIVES: The primary aim of this study was to evaluate whether there is a potential in vivo interaction between long- and short-acting beta2-agonists in the presence of increased airway tone induced by methacholine. In addition, a post hoc analysis was made to evaluate the effects of beta2-adrenoceptor polymorphisms. METHODS: Sixteen asthmatic subjects (mean age [+/-SD], 39 [13] years; FEV1, 81% [17%] of predicted value), all taking inhaled corticosteroids and having methacholine PD20 values of less than 500 micrograms, were randomized in double-blind, double-dummy, cross-over fashion to receive single doses of inhaled placebo, inhaled formoterol 12 micrograms, or inhaled salmeterol 50 micrograms followed 12 hours later by a single dose of inhaled albuterol 400 micrograms (low dose) or 1600 micrograms (high dose). Methacholine challenges were performed on each of 6 separate occasions 1 hour after albuterol. RESULTS: There was a greater numerical difference in geometric

mean PD20 values between low- and high-dose albuterol after placebo dosing (671 micrograms vs 1080 micrograms, a 1.61-fold difference; $P < .05$) compared with low- and high-dose albuterol after formoterol dosing (660 micrograms vs 799 micrograms, a 1.21-fold difference; $P = .4$), or after salmeterol dosing (568 micrograms vs 847 micrograms, a 1.49-fold difference; $P = .055$). PD20 values with high-dose albuterol in combination with formoterol or salmeterol were numerically lower than those found with high-dose albuterol in combination with placebo, but they were not significantly different. There was a significant difference between PD20 values with low-dose albuterol after dosing with formoterol (PD20 = 660 micrograms, a 1.6-fold difference; $P < .05$) or with salmeterol (PD20 = 568 micrograms, a 1.9-fold difference; $P < .05$) compared with PD20 with high-dose albuterol after placebo dosing (PD20 = 1080 micrograms). Post hoc polymorphism analysis for pooled pretreatment with formoterol and salmeterol (excluding placebo pretreatment) showed significantly ($P < .05$) lower PD20 values with homozygous glycine-16 compared with heterozygous glycine/arginine-16 and significantly ($P < .05$) lower PD20 values with homozygous glutamate-27 compared with either heterozygous glutamate/glutamine-27 or homozygous glutamine-27.

CONCLUSION: Compared with placebo, both salmeterol and formoterol caused a significant degree of antagonism of albuterol-induced bronchorelaxation in methacholine-contracted bronchi in vivo. This interaction could be caused by prolonged occupancy of airway beta2-adrenoceptors by long-acting beta2-agonists or by early tachyphylaxis 12 hours after a single-dose exposure. The degree of albuterol protection was also related to beta2-adrenoceptor polymorphism.

Article classification: RCT

AU: Wood, L. J., Sehmi, R., Gauvreau, G. M., Watson, R. M., Foley, R., Denburg, J. A., and O'byrne, P. M.

TI: An inhaled corticosteroid, budesonide, reduces baseline but not allergen-induced increases in bone marrow inflammatory cell progenitors in asthmatic subjects

SO: Am J Respir Crit Care Med

YR: 1999 May VL: 159 NO: 5 Pt 1 PG: 1457-63

UI: 99246479

AB: We have previously shown that allergen inhalation by asthmatics is associated with increases in bone marrow eosinophil/basophil colony-forming cells (Eo/B-CFU), and increases in CD34(+) hemopoietic progenitors expressing the alpha-subunit of the IL-5 receptor (IL-5Ralpha). This study investigated the effect of inhaled corticosteroid on baseline numbers and allergen-induced increases in these parameters. Nine subjects with mild, stable asthma inhaled budesonide (400 microgram/d) for 8 d in a placebo-controlled, double-blind, randomized crossover study. On Day 7, subjects inhaled allergen, with bone marrow sampling before and 24 h after challenge. Budesonide inhalation significantly attenuated the allergen-induced early and late asthmatic responses, degree of increase in sputum and blood eosinophils, as well as the baseline numbers of total bone marrow CD34(+) cells ($p < 0.05$), CD34(+)IL-3Ralpha+ cells ($p < 0.01$) and IL-5-responsive Eo/B-CFU ($p < 0.05$). Allergen inhalation significantly increased Eo/B-CFU grown in the presence of IL-3, GM-CSF, or IL-5 alone ($p < 0.05$) and in combination ($p < 0.01$), as well as the number of CD34(+)IL-5Ralpha+ cells ($p < 0.01$). However, these increases in Eo/B-CFU and CD34(+)IL-5Ralpha+ cells were not

affected by budesonide treatment. These data demonstrate that short-term inhaled budesonide treatment has a systemic effect in inhibiting the turnover of a subpopulation of bone-marrow-derived progenitors, but that inhalation of allergen overcomes this inhibitory effect.

Article classification: RCT

AU: Nath, R. P., Upton, R. A., Everhart, E. T., Cheung, P., Shwonek, P., Jones, R. T., and Mendelson, J. E.

TI: Buprenorphine pharmacokinetics: relative bioavailability of sublingual tablet and liquid formulations

SO: J Clin Pharmacol

YR: 1999 June VL: 39 NO: 6 PG: 619-23

UI: 99283393

AB: Buprenorphine is an effective new treatment for opiate dependence. This study compared the bioavailability of buprenorphine from a tablet to that from a reference solution. Six men experienced with, but not dependent on, opiates (DSM-III-R) were each administered 7.7 mg of buprenorphine in liquid form and 8 mg in tablet form 1 week apart in a balanced crossover design. Plasma levels were measured by electron capture capillary gas chromatography (GC), and concentration-time curves were constructed. Pharmacokinetic data were analyzed by analysis of variance. The bioavailability from the tablet was approximately 50% that from the liquid and was not affected by saliva pH. Lower bioavailability from the tablet may be due to slow dissolution.

Article classification: CCT

AU: Rittenhouse, B. E., Stinnett, A. A., Dulisse, B., Henke, C. J., Potter, L., Parasuraman, B., Martens, L. L., Williams, R. R., and Kojak, C.

TI: An economic evaluation of levofloxacin versus cefuroxime axetil in the outpatient treatment of adults with community-acquired pneumonia

SO: Am J Manag Care

YR: 2000 Mar. VL: 6 NO: 3 PG: 381-9

UI: 20364413

AB: **OBJECTIVE:** To examine treatment costs of community-acquired pneumonia (CAP) in adult outpatients given oral (p.o.) levofloxacin or cefuroxime axetil as initial therapy. **STUDY DESIGN:** Patients with a primary diagnosis of CAP were enrolled in a multicenter, prospective, randomized, open-label, active-controlled Phase III clinical trial. Both inpatients and outpatients were assigned to 1 of 2 treatment groups: (1) intravenous (i.v.) or p.o. levofloxacin; or (2) i.v. ceftriaxone and/or p.o. cefuroxime axetil. **METHODS:** To make legitimate and meaningful cost comparisons between similar types of patients receiving drugs via the same route of administration (i.e., orally), this outpatient economic study examined the resource utilization of the 211 patients enrolled as outpatients who received oral formulations as initial treatment (levofloxacin, 103 patients; cefuroxime axetil, 108 patients). Resource utilization data and clinical trial data were collected concurrently. To generate cost estimates, Medicare cost estimates for resources were multiplied by the resource units used by patients in each treatment arm. **RESULTS:** Cost estimates indicated a total cost difference that favored the levofloxacin

group (base case: \$169; sensitivity analysis: \$223 [P = .008]). The results for the base case were not significant (P = .094). In addition, within the cost categories, there was a statistically significant study drug cost differential favoring levofloxacin (\$86; P = .0001 for both the base case and sensitivity analysis). CONCLUSION: Oral levofloxacin is less costly than oral cefuroxime axetil in the outpatient treatment of adults with CAP.

Article classification: RCT

AU: Gibson, P. J., Koepsell, T. D., Diehr, P., and Hale, C.

TI: Increasing response rates for mailed surveys of Medicaid clients and other low-income populations

SO: Am J Epidemiol

YR: 1999 June VL: 149 NO: 11 PG: 1057-62

UI: 99281513

AB: Mailing surveys to low-income populations is often avoided because of concern about low response rates. In this study, the authors used a mailed survey of a low-income population to test whether \$1.00 or \$2.00 cash-response incentives were worth the expense and whether 2-day priority mail (\$2.90 postage) would yield a sufficiently higher response rate than certified mail (\$1.52 postage) to justify its cost. In 1994, 2,243 randomly selected families in subsidized health care programs in Pierce County, Washington, were randomly sent no incentive, \$1.00, or \$2.00 in the first of three mailings. For the third mailing, nonrespondents were randomly assigned to receive either certified or 2-day priority mail. After 4 weeks, the response rates were 36.7%, 48.1%, and 50.3% for the no-incentive, \$1.00, and \$2.00 groups, respectively. After three mailings, the cost per response was the lowest for the group that received \$1.00. The response rate for the certified mailing (28.1%) was significantly higher than the rate for the more expensive priority mailing (21.7%). No incentive-related bias was detected. The authors concluded that the most efficient protocol for this low-income population was to use a \$1.00 incentive in the first mailing and a certified third mailing.

Article classification: RCT

AU: Ackerman, S. J., Fokas, K. A., Monsein, L. H., and Ulatowski, J. A.

TI: Relationships among the subjective quality, magnetic resonance spectra, and price of wine: a randomized trial

SO: Acad Radiol

YR: 1995 Sept. VL: 2 NO: 9 PG: 822-6

UI: 98080917

AB: RATIONALE AND OBJECTIVES: We sought to discriminate among wines on the basis of three techniques: physical properties such as smell, taste, and quality; market price; and chemical analysis using proton nuclear magnetic resonance (MR) spectroscopy. METHODS: A randomized, double-masked, controlled crossover wine-tasting trial was conducted. Participants included seven men and seven women affiliated with an urban academic medical center, half of whom were physicians. The interventions consisted of eight red and eight white wines, including two respective, lower priced control wines. Each subject sampled all wines. Participants rated the overall quality of wine samples on a 5-point scale. The outcome measures were mean wine quality score, market price, and visual analysis of proton nuclear MR spectra.

RESULTS: One subject dropped out. Three white wines (p s = .0245, .0275, and .0425) and two red wines (p s = .0072 and .0128) were rated significantly higher than their respective, lower priced control wines. The mean wine quality score was not significantly correlated with market price (white wine, ρ = .371, p = .326; red wine, ρ = -.072, p = .8492). Visual analysis of proton nuclear MR spectra from the highest scoring wines and their respective control wines revealed more similarities than differences. CONCLUSION: Quality assurance of wine may best be left to the discriminating palate rather than market price or visual analysis of proton nuclear MR spectra.

Article classification: N/A

AU: Francis, D. P., Gregory, T., McElrath, M. J., Belshe, R. B., Gorse, G. J., Migasena, S., Kitayaporn, D., Pitisuttitham, P., Matthews, T., Schwartz, D. H., and Berman, P. W.

TI: Advancing AIDSVAX to phase 3. Safety, immunogenicity, and plans for phase 3

SO: AIDS Res Hum Retroviruses

YR: 1998 Oct. VL: 14 Suppl 3 PG: S325-31

UI: 99030126

AB: AIDSVAX (VaxGen, Inc., South San Francisco, CA), a possible vaccine to protect against human immunodeficiency virus type 1 (HIV-1) infection, is being tested for efficacy in phase 3 studies. It has been tested for potential efficacy in chimpanzees, and tested for safety and immunogenicity in human clinical studies. Four candidate vaccines, each with a different envelope protein antigen or combination of antigens, have been produced in alum formulations. In both design and clinical testing, AIDSVAX has an excellent safety profile. Because these highly purified proteins were prepared using recombinant DNA technology, there is no possibility of these vaccines causing HIV infection. Having been administered to over 1200 people, the only side effects attributable to AIDSVAX have been local pain and inflammation at the injection site. After immunization, essentially all recipients developed a robust antibody response, including binding and neutralizing antibodies. The neutralizing antibodies peaked after a 12-month boost. Excellent memory is induced. Two phase 3 trials of two bivalent formulations will evaluate their efficacy. One trial will use a bivalent subtype B formulation. This trial in North America will involve 5000 men who have sex with men and heterosexual women at high risk. The other study will use a bivalent subtype B/subtype E formulation. This trial in Thailand and will involve 2500 intravenous drug users. Both studies will be randomized, double-blinded and placebo controlled. The volunteers will be followed for 3 years. The end points of the studies are infection, as defined by seroconversion to standard diagnostic tests, and viral load, as defined by commercial polymerase chain reaction (PCR) tests.

Article classification: RCT

AU:

TI: Characteristics of patients with nonarteritic anterior ischemic optic neuropathy eligible for the Ischemic Optic Neuropathy Decompression Trial

SO: Arch Ophthalmol

YR: 1996 Nov. VL: 114 NO: 11 PG: 1366-74

UI: 97062279

AB: OBJECTIVE: To describe the baseline clinical characteristics of patients in the Ischemic Optic Neuropathy Decompression Trial (IONDT). DESIGN: The IONDT is a single-masked, multicenter, randomized clinical trial. SETTINGS: Twenty-five US clinical centers. PATIENTS: Eligibility criteria for randomization to either optic nerve sheath decompression surgery or careful follow-up included a diagnosis of acute unilateral nonarteritic anterior ischemic optic neuropathy (NAION), a visual acuity of 20/64 or worse and better than no light perception, and an age of 50 years or older. Patients who were eligible except for having visual acuity better than 20/64 were not randomized, but were followed up. METHODS: Each patient underwent a standardized history and examination by certified study personnel within 14 days of the onset of symptoms. Masked personnel performed outcome measurements. RESULTS: Of 420 patients with NAION, 258 were randomized, and 162 were not randomized and are being followed up. Sixty-two percent of the patients were men and 95% were white. The mean +/- SD age at onset was 66.0 +/- 8.7 years. Hypertension was reported in 47% of the patients in the IONDT, and 24% of the patients had diabetes mellitus. Forty-two percent of the patients recalled the onset of visual symptoms to be within 2 hours of awakening. Initial visual acuities in the study eye ranged from 20/20 or better to light perception, with 49% of the patients seeing better than 20/64 and 34% of the patients seeing 20/200 or worse. The mean Westergren sedimentation rate was 18.4 mm/h, with 9% of the patients having a rate greater than 40 mm/h. The nonrandomized patients (visual acuity better than 20/64) were younger, 72% were male, and they had a lower prevalence of hypertension and diabetes mellitus. CONCLUSION: Although our baseline findings are derived from a selected population of patients with NAION who were eligible for the IONDT, they provide the first description of NAION from a large prospective study that used a standard definition of NAION and only included patients who were identified within 2 weeks of the onset of symptoms.

Article classification: RCT

AU: Nabholz, J. M.

TI: Docetaxel (Taxotere) plus doxorubicin-based combinations: the evidence of activity in breast cancer

SO: Semin Oncol

YR: 1999 June VL: 26NO: 3 Suppl 9 PG: 7-13

UI: 99353496

AB: The high individual response rates of doxorubicin and docetaxel (Taxotere; Rhone-Poulenc Rorer, Collegeville, PA) as single agents in breast cancer and their lack of cross-resistance provide the rationale for investigation of the combination of these two uniquely acting agents. A dose-finding study defined the recommended doses for the combination given every 3 weeks as docetaxel 75 mg/m² plus doxorubicin 50 mg/m², or docetaxel 60 mg/m² plus doxorubicin 60 mg/m². Phase II studies conducted with these doses in first-line treatment of metastatic breast cancer patients resulted in overall response rates ranging between 57% and 77% with long durations of response. The high response rates were maintained in patients with unfavorable prognostic features, such as multiple metastatic disease sites, visceral involvement, and prior exposure to adjuvant chemotherapy. Without prophylactic G-CSF, grade 3/4 neutropenia and febrile neutropenia were the predominant hematologic toxicities. However, infectious

complications occurred infrequently. The nonhematologic toxicities of docetaxel and doxorubicin in combination are low in frequency and mild in severity. Additionally, the incidence of congestive heart failure was no greater than that expected with single-agent doxorubicin. The safety and efficacy results of these phase I and II trials appear to be confirmed in a randomized phase III trial comparing docetaxel plus doxorubicin versus doxorubicin plus cyclophosphamide in first-line metastatic breast cancer. Preliminary results reveal a superior overall response rate of 60% with docetaxel plus doxorubicin versus 47% with doxorubicin plus cyclophosphamide ($p = .008$). Time to disease progression and overall survival results are awaited. The results of these trials, in addition to others being conducted in the adjuvant and the neoadjuvant settings, will establish the ultimate place in therapy for the docetaxel and doxorubicin combination in the management of patients with breast cancer.

Article classification: RCT

AU: Shapiro, D. E., Sperling, R. S., Mandelbrot, L., Britto, P., and Cunningham, B. E.

TI: Risk factors for perinatal human immunodeficiency virus transmission in patients receiving zidovudine prophylaxis. Pediatric AIDS Clinical Trials Group protocol 076 Study Group

SO: Obstet Gynecol

YR: 1999 Dec. VL: 94 NO: 6 PG: 897-908

UI: 20041592

AB: **OBJECTIVE:** To identify modifiable obstetric factors associated with the failure of zidovudine chemoprophylaxis to prevent perinatal human immunodeficiency virus type 1 (HIV-1) transmission. **METHODS:** We analyzed data from Pediatric AIDS Clinical Trials Group protocol 076, a randomized, double-masked, placebo-controlled trial that demonstrated that a zidovudine regimen could prevent perinatal HIV-1 transmission. We estimated the zidovudine treatment effect using the relative reduction in transmission risk among women randomized to treatment with zidovudine compared with women randomized to receive placebo. Univariate and multivariate statistical analyses were used to assess whether the treatment effect differed in magnitude according to potential antepartum or intrapartum risk factors. **RESULTS:** In the univariate analysis, the zidovudine treatment effect was found to differ significantly in magnitude according to quartile of maternal weight at the time of study entry (interaction test, $P = .03$); among women in the heaviest-weight quartile (weight more than 82 kg), there was a 26% relative reduction in transmission risk, compared with a 79% relative reduction among the other three quartiles (interaction test, $P = .05$). In the zidovudine treatment group, women who transmitted HIV-1 were significantly more likely than nontransmitters to have had antepartum procedures or conditions associated with increased risk of fetal exposure to maternal blood or cervicovaginal secretions (43% compared with 19%, $P = .04$). In the multivariate analysis, adjustment for the plasma HIV-1 RNA level and CD4+ cell percentage did not eliminate the differential treatment effect according to these factors. **CONCLUSION:** High maternal weight and conditions associated with fetal exposure to maternal blood or cervicovaginal secretions may diminish the efficacy of zidovudine chemoprophylaxis.

Article classification: RCT

AU: Mamounas, E., Wieand, S., Wolmark, N., Bear, H. D., Atkins, J. N., Song, K., Jones, J., and Rockette, H.

TI: Comparative efficacy of adjuvant chemotherapy in patients with Dukes' B versus Dukes' C colon cancer: results from four National Surgical Adjuvant Breast and Bowel Project adjuvant studies (C-01, C-02, C-03, and C-04)

SO: J Clin Oncol

YR: 1999 May VL: 17 NO: 5 PG: 1349-55

UI: 99265687

AB: PURPOSE: Although the benefit from adjuvant chemotherapy has been clearly established in patients with Dukes' C colon cancer, such benefit has been questioned in patients with Dukes' B disease. To determine whether patients with Dukes' B disease benefit from adjuvant chemotherapy and to evaluate the magnitude of the benefit, compared with that observed in Dukes' C patients, we examined the relative efficacy of adjuvant chemotherapy according to Dukes' stage in four sequential National Surgical Adjuvant Breast and Bowel Project trials (C-01, C-02, C-03, and C-04) that compared different adjuvant chemotherapy regimens with each other or with no adjuvant treatment. PATIENTS AND METHODS: The four trials included Dukes' B and C patients and were conducted between 1977 and 1990. The eligibility criteria and follow-up requirements were similar for all four trials. Protocol C-01 compared adjuvant semustine, vincristine, and fluorouracil (5-FU) (MOF regimen) with operation alone. Protocol C-02 compared the perioperative administration of a portal venous infusion of 5-FU with operation alone. Protocol C-03 compared adjuvant 5-FU and leucovorin (LV) with adjuvant MOF. Protocol C-04 compared adjuvant 5-FU and LV with 5-FU and levamisole (LEV) and with the combination of 5-FU, LV, and LEV. RESULTS: Forty-one percent of the patients included in these four trials had resected Dukes' B tumors. In all four studies, the overall, disease-free, and recurrence-free survival improvement noted for all patients was evident in both Dukes' B and Dukes' C patients. When the relative efficacy of chemotherapy was examined, there was always an observed reduction in mortality, recurrence, or disease-free survival event, irrespective of Dukes' stage, and in most instances, the reduction was as great or greater for Dukes' B patients as for Dukes' C patients. When data from all four trials were examined in a combined analysis, the mortality reduction was 30% for Dukes' B patients versus 18% for Dukes' C patients. The mortality reduction in Dukes' B patients occurred irrespective of the presence or absence of adverse prognostic factors. CONCLUSION: Patients with Dukes' B colon cancer benefit from adjuvant chemotherapy and should be presented with this treatment option. Regardless of the presence or absence of other clinical prognostic factors, Dukes' B patients seem to benefit from chemotherapy administration.

Article classification: CCT

AU: Kieler, H., Hellberg, D., Nilsson, S., Waldenstrom, U., and Axelsson, O.

TI: Pregnancy outcome among non-participants in a trial on ultrasound screening

SO: Ultrasound Obstet Gynecol

YR: 1998 Feb. VL: 11 NO: 2 PG: 104-9

UI: 98211005

AB: Our objective was to characterize and evaluate pregnancy outcome in women who declined participation in a trial on ultrasound screening in the second trimester. Between

1985 and 1987, 8768 women were recruited for a trial on ultrasound screening. By randomization, 4997 women were assigned to either a screening or a non-screening group. Of the 1414 excluded women, data were retrieved from 1211 (86%). Participation was declined by 526 of these 1211 women, either because of anxiety regarding harmful effects of ultrasound or because they could see no benefits of ultrasound scanning. Non-participants and participants were compared. The non-participants were older, had a higher birth/pregnancy ratio, were less often smokers, and had fewer ultrasound examinations than the participants. There was a longer mean pregnancy length, an increased number of post-term deliveries, more suspicions of small-for-gestational-age fetuses and later detections of multiple pregnancies among non-participants as compared with the screening group. No differences in neonatal morbidity were found except for a greater number of mild respiratory disorders in the non-participant group. The non-participant women were more obstetrically experienced and showed indications of a healthier lifestyle in comparison with participants. The differences found in pregnancy outcome could be explained by the ultrasound screening procedure. There were no major differences in neonatal morbidity between the groups.

Article classification: RCT

AU: Grossman, J., Smith, L. J., Wilson, A. M., and Thyrum, P. T.

TI: Long-term safety and efficacy of zafirlukast in the treatment of asthma: interim results of an open-label extension trial

SO: Ann Allergy Asthma Immunol

YR: 1999 Apr. VL: 82 NO: 4 PG: 361-9

UI: 99241873

AB: BACKGROUND: Current guidelines recommend anti-leukotriene agents as alternative treatments for mild persistent asthma; however, information on their long-term safety and efficacy is needed. OBJECTIVE: To evaluate long-term safety and efficacy of and compliance with oral zafirlukast (Z; 20 mg BID) during the first 39 weeks of ongoing, multicenter, open-label extension (OLE) of a previously reported 13-week, randomized (2:1), double-blind (DB), placebo (P)-controlled trial in mild-to-moderate asthmatic patients treated previously with beta2-agonists alone. METHODS: Patients (12 to 76 years; FEV1 > or = 55% predicted) elected to enter OLE after completing the DB trial. Safety evaluated by adverse events (AEs), laboratory tests, and physical and electrocardiographic examinations. Efficacy assessed by spirometry measurements [FEV1, FEV1 % predicted, personal-best (post-bronchodilator) FEV1] and treatment failure rates. Compliance was calculated as percentage of treatment dispensed. After a visit at OLE week 3 (week 16), patients had visits every 12 weeks. RESULTS: A total of 443 patients (nz-->z = 310, np-->z = 133) entered the OLE. Results through the OLE period showed that 80% of patients overall reported AEs. Of patients randomized to Z and P during DB period, 68% and 67%, respectively, reported AEs during quarter I (Q1); percentage of Z-treated patients reporting AEs during the OLE ranged from 66% (Q2) to 44% (Q4). Review by quarters showed occurrence of AEs in Z-treated groups (Q2-4) was similar to that in P group (Q1). Compared with baseline (week 0), modest yet significant improvements ($P < \text{or} = .02$) in all spirometry measurements were noted in Z --> Z and P --> Z groups at OLE week 3, with sustained effects noted during OLE period. Treatment failure rates during OLE ranged from 7.2% (Q2) to 3.3% (Q4). Mean

compliance ranged from 98% (OLE week 3) to 95% (OLE week 39). CONCLUSIONS: Long-term treatment with zafirlukast was safe and well tolerated in asthmatic patients. Sustained efficacy and asthma control and good compliance were observed over extended treatment period. Results demonstrate long-term safety and effectiveness of and compliance with this anti-leukotriene agent.

Article classification: RCT

AU: Fleming, D. R., Glisson, S. D., Bhupalam, L., Michelson, G. D., Goldsmith, G. H., and LaRocca, R. V.

TI: Phase I study of paclitaxel and day 1/day 8 gemcitabine in patients with solid malignancies

SO: Am J Clin Oncol

YR: 2000 Aug. VL: 23NO: 4 PG: 349-52

UI: 20410828

AB: A phase I study was designed to evaluate the toxicity of escalating doses of gemcitabine along with fixed-dose paclitaxel in patients heavily pretreated with chemotherapy or radiotherapy. All patients had no prior therapy with the study drugs and possessed both adequate performance and end organ function. Eighteen patients were entered in the study. Characteristics included a median age of 66 years (range, 41 to 77) and stage IV disease in all patients; there were six patients with colon cancer, two with bladder cancer, three with non-small-cell lung cancer, two with esophageal cancer, three with pancreatic cancer, and two with cancer of unknown primary. Paclitaxel (150 mg/m² over 3 hours) was given on day 1 and gemcitabine (800, 900, and 1,000 mg/m² over 15 minutes) was given in three separate dose-escalating cohorts (1-3) on days 1 and 8. The treatment cycled every 21 days. The dose-limiting toxicity (DLT) proved to be neutropenia. All nonhematologic toxicities were mild and included gastrointestinal (nausea, vomiting, and diarrhea), dermatologic (rash), and neurologic (paresthesias) disturbances along with transient elevations of liver function tests. The combination of gemcitabine and paclitaxel seems to be well tolerated, and the recommended starting dose for a phase II study, in pretreated patients using a day 1/day 8 treatment schedule, should be 900 mg/m² for gemcitabine (days 1 and 8) along with 150 mg/m² for paclitaxel (day 1).

Article classification: N/A

AU: de Jonge, M. J., Loos, W. J., Gelderblom, H., Planting, A. S., van der Burg, M. E., Sparreboom, A., Brouwer, E., van Beurden, V., Mantel, M. A., Doyle, E., Hearn, S., Ross, G., and Verweij, J.

TI: Phase I pharmacologic study of oral topotecan and intravenous cisplatin: sequence-dependent hematologic side effects

SO: J Clin Oncol

YR: 2000 May VL: 18NO: 10 PG: 2104-15

UI: 20272000

AB: PURPOSE: In in vitro studies, synergism and sequence-dependent effects were reported for the combination of topotecan and cisplatin. Recently, an oral formulation of topotecan became available. This phase I study was performed to assess the feasibility of the combination of oral topotecan and cisplatin, the pharmacokinetic interaction, and

sequence-dependent effects. PATIENTS AND METHODS: Topotecan was administered orally (PO) daily for 5 days in escalating doses and cisplatin was given intravenously (IV) at a fixed dose of 75 mg/m² either before topotecan administration on day 1 (sequence CT) or after topotecan administration on day 5 (sequence TC) once every 3 weeks. Patients were treated in a randomized cross-over design. RESULTS: Forty-nine patients were entered onto the study; one patient was not eligible. Sequence CT induced significantly more severe myelosuppression than did sequence TC, and the maximum-tolerated dosage of topotecan in sequence CT was 1.25 mg/m²/d x 5. In sequence TC, the maximum-tolerated dosage of topotecan was 2.0 mg/m²/d x 5. Dose-limiting toxicity consisted of myelosuppression and diarrhea. Pharmacokinetics of topotecan and cisplatin were linear over the dose range studied; no sequence-dependent effects were observed. In addition, topotecan did not influence the protein binding of cisplatin or the platinum-DNA adduct formation in peripheral leukocytes in either sequence. CONCLUSION: The recommended dosages for phase II studies involving patients like the patients in our study are topotecan 1.25 mg/m²/d PO x 5 preceded by cisplatin 75 mg/m² IV day 1 once every 3 weeks, and topotecan 2.0 mg/m²/d PO followed by cisplatin 75 mg/m² IV day 5. No pharmacokinetic interaction could be discerned in our study. The antitumor efficacy of both schedules should be evaluated in a randomized phase II study.

Article classification: RCT

AU: Innocenti, F., Stadler, W. M., Iyer, L., Ramirez, J., Vokes, E. E., and Ratain, M. J.

TI: Flavopiridol metabolism in cancer patients is associated with the occurrence of diarrhea

SO: Clin Cancer Res

YR: 2000 Sept. VL: 6 NO: 9 PG: 3400-5

UI: 20452350

AB: Flavopiridol, a cyclin-dependent kinase inhibitor currently undergoing clinical evaluation, has a dose-limiting toxicity of diarrhea. Preclinical data on flavopiridol metabolism indicate that flavopiridol undergoes hepatic glucuronidation. The purpose of this study is to evaluate whether the occurrence of diarrhea is related to the systemic glucuronidation of flavopiridol. Parent drug and metabolite concentrations in plasma were measured by high-pressure liquid chromatography in 22 metastatic renal cancer patients treated on a Phase II trial of 50 mg/m²/day of flavopiridol administered every 2 weeks as a 72-h continuous infusion. Pharmacokinetics of flavopiridol and its glucuronide were assessed during the first cycle at 23, 47, and 71 h during the infusion. Flavopiridol concentrations at 23, 47, and 71 h were 389 nM (296-567 nM), 412 nM (297-566 nM), and 397 nM (303-597 nM) [median (interquartile range)], respectively. Flavopiridol glucuronide reached a plateau of 358 nM (196-553 nM) at 47 h. Metabolic ratios of flavopiridol glucuronide:flavopiridol at 71 h showed an apparent bimodal distribution with an antimode of 1.2. Thirteen patients experienced diarrhea and had lower metabolic ratios [0.72 (0.53-0.86)] than patients without diarrhea [2.24 (1.76-2.3); P = 0.002]. Eight of 11 extensive glucuronidators (ratio > 1.2) did not develop diarrhea, whereas 10 of 11 poor glucuronidators (ratio < 1.2) developed diarrhea (P = 0.008). The glucuronidation of flavopiridol is apparently polymorphic, suggesting a genetic etiology.

The systemic glucuronidation of flavopiridol is inversely associated with the risk of developing diarrhea.

Article classification: N/A

AU: van Toorn, D. W., Nortier, J. W., Rubach, M., de Swart, C. A., Huldij, J. C., van Tinteren, H., and Vermorke, J. B.

TI: Randomized phase II study of FEC day 1 + 8 and FEC day 1 in patients with advanced breast cancer

SO: Breast Cancer Res Treat

YR: 2000 Mar. VL: 60 NO: 1 PG: 57-62

UI: 20302464

AB: BACKGROUND: Dose-intensive chemotherapy regimens without stem cell support have not resulted in an improved survival compared to standard dose regimens in patients with metastatic breast cancer. Combinations of an anthracycline, cyclophosphamide and 5 fluorouracil are still standard in such patients. The aim of this study was to investigate the two different schedules of epirubicin in a standard dose FEC regimen with respect to response and toxicity. MATERIALS AND METHODS: Patients were randomly assigned to receive a day 1 + 8 schedule (5FU and CTX 500mg/m² day 1, epirubicin 40 mg/m² day 1 and 8) or a day 1 schedule (5FU, CTX 500 mg/m² and epirubicin 80 mg/m² day 1), q day 21, both given without hematopoietic growth factors. A total of 104 eligible patients were analyzed, 52 in each arm. RESULTS AND CONCLUSIONS: A significantly higher relative dose-intensity was found for the day 1 schedule compared to the day 1 + 8 schedule. Although the trial was not set up to reliably detect a difference in response rate, this difference in relative dose-intensity in favour of the day 1 schedule does not suggest any improvement in response rate or duration of response for the day 1 schedule. Myelosuppression was severe in the day 1 + 8 schedule. We conclude that a day 1 + 8 FEC schedule has no advantage over a day 1 FEC schedule without hematopoietic growth factors in patients with metastatic breast cancer.

Article classification: RCT

AU: Motzer, R. J., Murphy, B. A., Bacik, J., Schwartz, L. H., Nanus, D. M., Mariani, T., Loehrer, P., Wilding, G., Fairclough, D. L., Cella, D., and Mazumdar, M.

TI: Phase III trial of interferon alfa-2a with or without 13-cis-retinoic acid for patients with advanced renal cell carcinoma

SO: J Clin Oncol

YR: 2000 Aug. VL: 18 NO: 16 PG: 2972-80

UI: 20402471

AB: PURPOSE: A randomized phase III trial was conducted to determine whether combination therapy with 13-cis-retinoic acid (13-CRA) plus interferon alfa-2a (IFNalpha2a) is superior to IFNalpha2a alone in patients with advanced renal cell carcinoma (RCC). PATIENTS AND METHODS: Two hundred eighty-four patients were randomized to treatment with IFNalpha2a plus 13-CRA or treatment with IFNalpha2a alone. IFNalpha2a was given daily subcutaneously, starting at a dose of 3 million units (MU). The dose was escalated every 7 days from 3 to 9 MU (by increments of 3 MU), unless \geq grade 2 toxicity occurred, in which case dose escalation was stopped.

Patients randomized to combination therapy were given oral 13-CRA 1 mg/kg/d plus IFNalpha2a. Quality of life (QOL) was assessed. RESULTS: Complete or partial responses were achieved by 12% of patients treated with IFNalpha2a plus 13-CRA and 6% of patients treated with IFNalpha2a (P =.14). Median duration of response (complete and partial combined) in the group treated with the combination was 33 months (range, 9 to 50 months), versus 22 months (range, 5 to 38 months) for the second group (P =.03). Nineteen percent of patients treated with IFNalpha2a plus 13-CRA were progression-free at 24 months, compared with 10% of patients treated with IFNalpha2a alone (P =.05). Median survival time for all patients was 15 months, with no difference in survival between the two treatment arms (P =.26). QOL decreased during the first 8 weeks of treatment, and a partial recovery followed. Lower scores were associated with the combination therapy. CONCLUSION: Response proportion and survival did not improve significantly with the addition of 13-CRA to IFNalpha2a therapy in patients with advanced RCC. 13-CRA may lengthen response to IFNalpha2a therapy in patients with IFNalpha2a-sensitive tumors. Treatment, particularly the combination therapy, was associated with a decrease in QOL.

Article classification: RCT

AU: Xu, B., Zhou, J., and Zhou, A.

TI: [Phase III clinical studies with ondansetron (Qilu) in the prophylaxis of nausea and vomiting induced by cisplatin]

SO: Chung Hua Chung Liu Tsa Chih

YR: 1997 Sept. VL: 19NO: 5 PG: 358-61

UI: 20376330

AB: OBJECTIVE: To further evaluate the clinical usefulness of ondansetron(OND, supplied by Qilu Pharmaceutical Company) with modified regime in the prevention of cisplatin (DDP)-induced nausea and vomiting. METHODS: A total of 773 patients were enrolled in a multicenter cooperative study. Of them, 330 patients were given i.v. OND 8 mg once or twice a day and 443 patients were given i.v. OND 8 mg plus dexamethasone(DXM) 10 mg once a day during the therapeutic period of DDP, followed by OND 4 mg orally twice a day for two days after DDP treatment. RESULTS: Effective control of acute nausea was achieved in 86.7% and 94.8% of the patients receiving OND alone and OND plus DXM, respectively(P < 0.001). The mean frequency of vomiting was 0.9 times in OND and 0.4 times in OND plus DXM(P < 0.01). Total control of delayed vomiting (day 2-5) was comparable in both groups. Complete inhibition of vomiting (CR rate) was more frequently observed in males than in females. Adverse effects were identical and well tolerated. CONCLUSION: OND with modified regimen is effective in the control of DDP-induced vomiting. It is more effective when OND and DXM are given than OND given alone.

Article classification: CCT

AU: Haw, W. W. and Manche, E. E.

TI: One-year evaluation of myopic laser photoastigmatic refractive keratectomy using the summit apex plus: phase III of a Food and Drug Administration clinical trial

SO: Ophthalmology

YR: 2000 Aug. VL: 107 NO: 8 PG: 1572-7

UI: 20381479

AB: PURPOSE: To prospectively evaluate the safety and efficacy of the Summit Apex Plus excimer laser in the treatment of primary compound myopic astigmatism. DESIGN: Prospective noncomparative interventional case series. PARTICIPANTS: Patients with primary compound myopic astigmatism: sphere of -1.0 to -7.0 diopters (D) and cylinder -1.0 to -5.0 D. METHODS: Ninety-three eyes of 56 patients with a mean spherical equivalent of -4.98 ± 1.80 D (-1.75 to -8.5) underwent photoastigmatic refractive keratectomy (PARK) with the Summit Apex Plus excimer laser using erodible mask technology. Prospective follow-up is analyzed at 1-year postoperatively. MAIN OUTCOME MEASURES: Postoperative reduction in myopic sphere, myopic astigmatism, spherical equivalent, angle of error, magnitude of error, difference vector, uncorrected visual acuity, and corneal haze. RESULTS: Seventy-one eyes were available at 1-year follow-up. Mean spherical equivalent was reduced 86.5% to a mean residual of -0.65 D ± 0.70 D (-2.88-+1.13 D). Astigmatism was reduced 66.2% to a mean residual of -0.76 ± 0.52 D (-2.25-0.00 D); 77.5% were within 1.0 D of attempted correction; 1.4% of eyes experienced an overcorrection >1.0 D of spherical equivalent; 0.27 D of mean myopic regression was demonstrated between 1 and 12 months; 93.0% of eyes achieved an uncorrected visual acuity of 20/40 or better; and 49.3% of eyes achieved an uncorrected visual acuity of 20/20 or better. CONCLUSIONS: PARK with the Summit Apex Plus excimer laser is effective at reducing compound myopic astigmatism. However, current laser algorithms result in consistent undercorrection of both the compound myopia and the astigmatic component.

Article classification: N/A

AU: Guerrini, S., Lualdi, P., and Biffignandi, P.

TI: Treatment of venous leg ulcers with 5% amikacin gel: phase IV trial

SO: Int J Clin Pharmacol Res

YR: 1999 VL: 19 NO: 1 PG: 35-8

UI: 99379035

AB: A phase IV trial with 5% amikacin gel was carried out on 100 adult in patients of both sexes suffering from venous infected leg ulcers. After 2 weeks' therapy the microbiological culture tests were negative for more than 80% of the patients. The mean ulcer surface area was reduced by 34% and the accompanying symptoms of erythema, inflammation and pain were improved. Only very mild unwanted local effects were reported by four out of the 100 patients. Five percent amikacin gel was judged a safe and effective topical treatment for curing infected venous leg ulcers.

Article classification: N/A

AU: Boissel, J. P., Meillard, O., Perrin-Fayolle, E., Ducruet, T., Alamertery, Y., Sassano, P., and Benghozi, R.

TI: [Example of a phase IV trial involving several physicians and aiming at answering a scientific question: EOL]

SO: Therapie

YR: 1996 Nov.-1996 Dec. VL: 51 NO: 6 PG: 667-76

UI: 97306736

AB: The aim of this trial was to test the hypothesis that a reduced number of doses improves compliance in current medical practice. Compliance with twice a day dosage was compared with compliance with three doses a day. Two bioequivalent presentations of nicardipine were used, the regular presentation (t.i.d.) and the slow-release (b.i.d.). The trial was controlled, randomized, open, in two parallel groups: (1)'t.i.d.' group: one tablet of regular nicardipine, 20 mg, three times a day, three months; (2) 'b.i.d.' group: one capsule of slow-release nicardipine, twice a day, three months. 2651 general practitioners randomized 7274 hypertensive patients. The primary criterion was documented in 93.7 per cent of the cases at the end of the trial. The remaining 6.3 per cent comprised treatment withdrawal (2.8 per cent) and patients lost to follow-up (3.5 per cent). The primary criterion study was compliance, assessed by a self-questionnaire filled in by the patient and a standardised interview by the physician. Compliance was slightly better in the b.i.d. group than in the t.i.d. group ($p < 0.001$). Remaining pill count was also used but it was a failure. A random sample of investigators made on-site visits. Discordant data were infrequent and were limited to dates of visits. Difficulties with on-site visits were mostly due to a rather frequent lack of source records.

Article classification: RCT

AU: Barrett, B., Vohmann, M., and Calabrese, C.

TI: Echinacea for upper respiratory infection

SO: J Fam Pract

YR: 1999 Aug. VL: 48NO: 8 PG: 628-35

UI: 99424961

AB: **OBJECTIVES:** To review the evidence regarding the effectiveness of orally ingested Echinacea extracts in reducing the incidence, severity, or duration of acute upper respiratory infections (URIs). **SEARCH STRATEGIES:** Information from a wide range of sources was used as background material. More than 100 articles, books, and book chapters were reviewed for content and further references. Database searches, bibliographic reviews, and conversations with experts were carried out iteratively from January 1997 to February 1999. **SELECTION CRITERIA:** Published or unpublished reports of all blinded placebo-controlled randomized trials of any Echinacea formulation used as a treatment or for the prevention of URIs. **DATA COLLECTION AND ANALYSIS:** Review considerations included randomization, blinding, power, validity and clinical relevance of outcome measurements, inclusion and exclusion criteria, indistinguishability of treatment and placebo, and appropriateness of conclusions for the data presented. **MAIN RESULTS.** Nine treatment trials and 4 prevention trials fitting the selection criteria were found. Eight of the treatment trials reported generally positive results, and 3 of the prevention trials reported marginal benefit. Methodologic quality of the majority of the trials was modest. **CONCLUSIONS:** Evidence from published trials suggests that Echinacea may be beneficial for the early treatment of acute URIs. The influence of publication bias on those results is unknown. Echinacea preparations vary widely in composition, and are often found in combination with other potentially active constituents, making specific dose recommendations problematic. There is very little evidence supporting the prolonged use of Echinacea for the prevention of URIs.

Article classification: N/A

AU: Campbell, R. K., Campbell, L. K., and White, J. R.

TI: Insulin lispro: its role in the treatment of diabetes mellitus

SO: Ann Pharmacother

YR: 1996 Nov. VL: 30 NO: 11 PG: 1263-71

UI: 97070483

AB: OBJECTIVE: To introduce a rapid-acting human insulin analog, insulin lispro; to review its pharmacology, therapeutics, pharmacokinetics, dosing guidelines, adverse effects, and drug interactions; and to summarize the clinical trials of its efficacy and safety alone and in comparison with regular human insulin in the treatment of diabetes mellitus. DATA SOURCES: A MEDLINE database search was completed to identify all relevant articles, including reviews; Eli Lilly and Co.; published articles and abstracts; and review chapters from medical textbooks. STUDY SELECTION: Due to the relatively few citations listed in MEDLINE (12 as of December 1995), most of the studies reported were found from abstracts summarizing the clinical action, adverse effects, or pharmacokinetics of insulin lispro in healthy volunteers or patients with diabetes mellitus. A few of the studies used patients with diabetes mellitus in multicenter, randomized, crossover trials of insulin lispro. DATA EXTRACTION: All clinical trials that were available prior to submission of this manuscript for publication, including unpublished reports, were reviewed. DATA SYNTHESIS: The human insulin analog, insulin lispro, which is biosynthetically made by inverting the amino acid sequence of human insulin at B-28 and B-29, is more effective than regular human insulin in improving postprandial glucose control. Subcutaneous injections of insulin lispro result in decreased blood glucose peaks following meals and a potential decreased risk of hypoglycemic episodes, including nighttime hypoglycemia in patients with type 1 diabetes. Insulin lispro in comparison with regular human insulin provides equal or slightly better blood glucose control. When compared with subcutaneous injections of regular human insulin, the peak serum insulin concentration of insulin lispro is three times higher, time to peak is 4.2 times faster, the absorption rate constant is double, and the duration of action is half as long. Insulin lispro is similar to regular human insulin with reference to dose, toxicity, adverse effects, drug interactions, and immunogenicity. When insulin lispro is mixed with human NPH (isophane) or Lente insulins, insulin lispro should be drawn into the syringe first, mixed with the long-acting insulin, and injected immediately after mixing. Patients using insulin lispro perceive an improvement in their well-being and quality of life due to flexible injection times and less frequent hypoglycemic reactions. Insulin lispro is believed to be suitable for patients using insulin infusion pumps. CONCLUSIONS: Insulin lispro is equipotent to human insulin and has a much more rapid onset and shorter duration of action than human insulin does, which may reduce the risk of hypoglycemia. In addition, insulin lispro improves the dosing convenience for patients with diabetes and provides a more natural control of blood glucose concentrations. Insulin lispro is a useful new agent in the treatment of diabetes mellitus.

Article classification: N/A

AU: Grossman, E., Messerli, F. H., and Goldbourt, U.

TI: High blood pressure and diabetes mellitus: are all antihypertensive drugs created equal?

SO: Arch Intern Med

YR: 2000 Sept. VL: 160 NO: 16 PG: 2447-52

UI: 20435210

AB: OBJECTIVE: To analyze the available data to assess the benefits of antihypertensive therapy in hypertensive patients with diabetes mellitus. METHODS: A MEDLINE search of English-language articles published until June 1999 was undertaken with the use of the terms diabetes mellitus, hypertension or blood pressure, and therapy. Pertinent articles cited in the identified reports were also reviewed. Included were only prospective randomized studies of more than 12 months' duration that evaluated the effect of drug treatment on morbidity and mortality in diabetic hypertensive patients. We estimated the risk associated with combination of diabetes mellitus and hypertension and the effect of treatment on morbidity and mortality. RESULTS: The coexistence of diabetes mellitus doubled the risk of cardiovascular events, cardiovascular mortality, and total mortality in hypertensive patients (approximate relative risk of 1.73-2.77 for cardiovascular events, 2.25-3.66 for cardiovascular mortality, and 1.73-2.18 for total mortality). Intensive blood pressure control to levels lower than 130/85 mm Hg was beneficial in diabetic hypertensive patients. All 4 drug classes-diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, and calcium antagonists-were effective in reducing cardiovascular events in diabetic hypertensive patients. In elderly diabetic patients with isolated systolic hypertension, calcium antagonists reduced the rate of cardiac end points by 63%, stroke by 73%, and total mortality by 55%. In more than 60% of diabetic hypertensive patients, combination therapy was required to control blood pressure. CONCLUSIONS: Intensive control of blood pressure reduced cardiovascular morbidity and mortality in diabetic patients regardless of whether low-dose diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, or calcium antagonists were used as a first-line treatment. A combination of more than 1 drug is frequently required to control blood pressure and may be more beneficial than monotherapy.

Article classification: N/A

AU: Jadad, A. R., Carroll, D., Glynn, C. J., and McQuay, H. J.

TI: Intravenous regional sympathetic blockade for pain relief in reflex sympathetic dystrophy: a systematic review and a randomized, double-blind crossover study

SO: J Pain Symptom Manage

YR: 1995 Jan. VL: 10 NO: 1 PG: 13-20

UI: 95230091

AB: The first aim was a systematic review of intravenous regional sympathetic blocks (IRSBs) in patients with reflex sympathetic dystrophy (RSD). Randomized controlled trials (RCTs) of IRSBs in patients with RSD were identified by MEDLINE search (1966 to May 1993) and by hand search of 30 journals (1950 to May 1993). Authors of eligible trials were asked for information on additional trials and for unpublished data. Seven RCTs of IRSBs in RSD were found. Four used guanethidine; none showed significant analgesic effect in IRSBs to relieve pain due to RSD. Two reports, one using ketanserin and one bretylium, with 17 patients in total, showed some advantage of IRSBs over

control. RCT results were not combined because of the variety of different drugs and outcome measures and because of methodological deficiencies in most of the reports. The second aim was a randomized, double-blind, crossover study to assess the effectiveness of IRSBs with guanethidine. Patients fulfilling diagnostic criteria for RSD and who had reported pain relief after an open IRSB with guanethidine received IRSBs with guanethidine high dose, guanethidine low dose, and normal saline. Pain intensity and relief, adverse effects, mood, duration of analgesia, and global scores were recorded. Sixteen patients with diagnosis of RSD were recruited, but only nine entered the double-blind phase. The trial was stopped prematurely because of the severity of the adverse effects. No significant difference was found between guanethidine and placebo on any of the outcome measures.(ABSTRACT TRUNCATED AT 250 WORDS)

Article classification: RCT