including imaging studies of the liver to assess right lobe volume; and
4. Ancillary testing precipitated by abnormalities of earlier tests.

Of 100 potential recipients, 51 were initially rejected based on recipient characteristics, including imminent cadaveric transplantation (n = 8), refused of evaluation (n = 4), lack of financial approval (n = 6), and medical, psychosocial, or surgical problems (n = 33).

Of the remaining 49 patients, 24 were unable to identify a suitable donor. Twenty-six donors were evaluated for the remaining 25 transplant recipients. Eleven were rejected (9 for medical reasons, and 2 refused donation after approval); the remaining 15 donor-recipient pairs underwent LDLT. The Colorado investigators concluded that recipient and donor characteristics limit the widespread use of LDLT, and thus the impact of LDLT on the major discrepancy between potential recipients and available cadaveric organs (17,000 vs 4,700) will likely be small.

In patients with acute liver failure, the progression to death occurs over the course of a few days or weeks; the use of LDLT in this setting is dramatic.

Consensus Statement on the Live Organ Donor

Authors for the Live Organ Donor Consensus Group.

JAMA. 2000;284:2919-2926.

The majority of living donors for pediatric patients are parents, and their voluntary intention is easily understood and justified. However, in the case of adult LDLT, the higher risk of the more extensive donor operation and the more complex social interrelationships for nonparental donors make the process of evaluation and consent for adult-to-adult LDLT more complex. A recent executive group representing all constituencies involved with living donor transplantation of the kidney, pancreas, liver, intestine and lung met and developed a consensus statement that was recently published. The key message was that the person who gives consent to be a live organ donor should be competent, willing to donate, free from coercion, medically and psychosocially suitable, fully informed of the risks and benefits as a donor, and fully informed of the risks, benefits and alternative treatment available to the recipient. Important elements of disclosure to the potential donor include: description of the evaluation, surgical procedure, and postoperative period; anticipated short-term and long-term care; alternative donation procedures; potential surgical complications, including death; any expenses to be borne by the donor; potential impact on ability to obtain health and life insurance; potential impact on lifestyle and ability to obtain future employment; and all details regarding the recipient, including center-specific statistics. Use of a minor (<18 years of age) remains controversial and requires careful donor consideration. A nondirected (also referred to as "Good Samaritan") donor should meet the same criteria as those applied to directed donation, with special attention to psychosocial issues. The group also felt that the psychosocial and medical evaluation of the donor should be coordinated by a mental health professional and internist not involved in the care of the potential recipient. Finally, there was broad support for the development of a live organ donor registry.

The ultimate impact of adult LDLT on liver transplantation will depend largely on donor safety and the success of recipient surgery, as well as on the proportion of cadaveric recipients who are deemed suitable for LDLT. For widespread acceptance of adult-to-adult LDLT, the graft and patient survival rates must be comparable to cadaveric transplantation, and the morbidity and mortality of living donors must remain minimal as LDLT is applied more broadly. The most appropriate recipients for adult-to-adult LDLT appear to be status 2B patients with decompensated advanced liver disease or status 1 patients with acute hepatic failure. In addition, patients with a small HCC likely to be curable by liver transplantation if performed in a timely fashion and patients with primary sclerosing cholangitis at increased risk of cholangiocarcinoma are excellent candidates for LDLT. With greater experience, the indications for LDLT recipient selection may broaden to include a greater proportion of patients currently listed for cadaveric transplantation.

Crohn's Disease

Maintenance Therapies for Crohn's Disease

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Crohn's disease is a chronic, relapsing inflammatory bowel disease. Therapy has aimed at treating active disease, although recently defined goals call for inducing or maintaining clinical remissions. It has become

increasingly apparent that not only are the disease patterns and presentations heterogeneous, but also the effectiveness of maintenance therapies depends, to some extent, on the treatment used to induce remissions.

To date, corticosteroids, while most commonly used to gain remissions, have not proved effective in maintaining them. Most patients—up to 75% or 80%—remain ill, relapse or are steroid-dependent after an 8-12 week course of prednisone[1] or controlled release budesonide.[2] Mesalamine has been evaluated for maintenance therapy of Crohn's disease and has not proved effective at maintaining steroid-induced remissions.[3] It may, however, have some benefits after mesalamine-induced remissions[4] and after surgical resection.[5] In contrast, the purine antimetabolites, azathioprine and 6-mercaptopurine (6-MP), have had both steroid-sparing and maintenance benefits in controlled trials.[6]

This review focuses on some reports on recent clinical trials that have assessed maintenance therapies for Crohn's disease in specific clinical scenarios that help to define the long-term approach to treatment of children with Crohn's disease and determine the efficacy and safety of long-term methotrexate. This research affords additional data regarding the management of post-operative Crohn's disease.

A Multicenter Trial of 6-Mercaptopurine and Prednisone in Children with Newly Diagnosed Crohn's Disease

Markowitz J, Grancher K, Kohn N, et al.
Gastroenterology. 2000;119:895-902

Previous clinical trials have demonstrated a steroid-sparing and maintenance benefit from azathioprine, 2.5 mg/kg, in adult patients with Crohn's disease. In this clinical trial 55 children (mean age 13) with newly diagnosed Crohn's disease of moderate to severe disease activity were randomized to receive an eight-week course of tapering prednisone beginning at 40 mg daily either with placebo or 6-mercaptopurine, 1.5 mg/kg. Prednisone dosage was adjusted according to clinical activity and tapered after clinical remission was achieved. Patients were followed for 18 months and were assessed by clinical disease activity score and prednisone usage. There were no significant differences in the group ages, gender, site of disease, or activity.

Results of the trial demonstrated that 89% of both groups achieved short term remissions with the steroids, however, only 9% of the 6-MP group compared to 47% of the control group relapsed during the 18 months of follow-up. No clinically significant adverse events were observed aside from mild leukopenia and increases in the aminotransferase activity in the 6-MP group. The investigators concluded that the addition of 6-MP to a regimen of corticosteroids significantly reduces the need for steroids and maintains remissions after steroid-induction in newly diagnosed children with moderate to severe Crohn's disease.

A Comparison of Methotrexate with Placebo for Maintenance of Remission in Crohn's Disease

Feagan BG, Fedorak RN, Irvine EJ, et al.
N. Engl. J. Med. 2000;342:1627-1632

This North American Study group had previously demonstrated that parenteral methotrexate, 25 mg/week, allowed steroid-dependent patients to maintain remission while tapering steroids over a 10-16 week interval. However, long-term safety and efficacy of methotrexate had not been established. Therefore, as a follow-up trial, the investigators enrolled patients who had entered remission on methotrexate in the "acute trial" as well as patients who had achieved remissions on "open-label" methotrexate over 16-24 weeks into a randomized maintenance trial.

Patients were randomized to receive either methotrexate 15 mg, intramuscularly, weekly or placebo for 40 weeks. The end-point was the proportion of patients who remained in remission defined as a Crohn's Disease Activity Index (CDAI) score of less than 150. A total of 76 patients were entered, with 40 receiving methotrexate and 36 placebo injections. There were no significant baseline differences between the groups. After 40 weeks, 65% of patients receiving methotrexate remained in remission, compared to 39% of patients randomized to placebo. In addition, fewer patients in the methotrexate group required prednisone for relapse. None of the patients who received methotrexate had a serious adverse event.

The investigators concluded that 15 mg of methotrexate maintained remissions over 40 weeks in patients who had initially responded to methotrexate.

Prophylaxis of Postoperative Relapse in Crohn's Disease with Mesalamine: European Cooperative Crohn's Disease Study VI

Lochs H, Mayer M, Fleig WE, et al.
Gastroenterology. 2000;118:264-273

There have been a series of clinical trials evaluating mesalamine as a post-operative therapy to prevent relapse after intestinal resections in Crohn's disease. These studies have examined different doses and delivery systems for the aminosalicylate.

The current trial is the largest to date, enrolling 318 patients after intestinal resection to receive 4 g/day of controlled-release mesalamine (Pentasa®) or placebo for

18 months. The primary outcome measure was defined as a relapse according to the CDAI, re-operation, septic complication, or new fistula. The cumulative relapse rates after 18 months were 24% in the mesalamine group versus 31% in the placebo group (P = .10). However, retrospective analysis demonstrated that patients with isolated small bowel disease had an improved outcome with mesalamine with relapse occurring in 22% compared to 40% in the placebo group (P = .02). Risk factors for recurrence included short-duration of disease and the use of steroids before surgery.

The investigators concluded that although mesalamine, 4 g/day, did not significantly affect the postoperative course of Crohn's disease, some effect was found in patients with isolated disease.

Summary

Crohn's disease remains a heterogeneous condition with different patterns of disease location, course, and activity (inflammatory, fibrostenotic, fistulizing). In addition, exogenous factors such as cigarette smoking can affect the course and responsiveness of disease to medical or surgical intervention: smokers, particularly females, have a worse response to treatment and a higher likelihood of postoperative relapse.

It also appears that a patient's response to acute therapy may have consequences for the subsequent responsiveness to maintenance therapies. For instance, corticosteroid therapy does not prolong remissions in Crohn's disease[1,2] and patients who require steroids to enter remission are unlikely to respond to mesalamine maintenance therapy.[3] In contrast, several trials have demonstrated that the purine analogues, azathioprine and 6-MP can prolong remissions while allowing steroid withdrawal.[7-9] What remains to be clarified is the optimal dosing of these agents for both safety and efficacy. With the ability to measure both the thiopurine transferase enzyme and metabolites such as 6-thioguanine nucleotides (the focus of a future review) we may be on the verge of specific therapeutic drug monitoring rather than dosing according to weight or leukocyte counts.

The trial by Markowitz et al adds support for the early administration of immunomodulators for Crohn's disease and presents the best results, to date, for treatment with purine analogues. The trial design was similar to the study by Candy et al,[7] and found no difference in the first three months of steroid-therapy whether or not patients were started on 6-MP. These results are consistent with the message proposed by Present and Korelitz, that it requires 3-6 months for these drugs to take effect.[9] Of interest, however, was the magnitude of effect in the Markowitz trial. Only 42% of the adults in the Candy trial remained in remission at 15 months compared to 7% of patients receiving placebo. There were substantially more responders to both 6-MP and placebo in the Markowitz trial although the ARR approximated 35% (NNT of approximately 3) in each

It also appears that a patient's response to acute therapy may have consequences for the subsequent responsiveness to maintenance therapies.

Table
Effect of Drugs on Remission/Relapse of Patients with Crohn's Disease

	Control (Placebo) Group (%)	Group Receiving Drug (%)
6-Mercaptopurine and Prednisone*		
Achieving short-term remission	89	89
Relapsing during 18-month follow-up	47	9
Methotrexate†		
In remission after 40 weeks	39	65
Mesalamine‡		
Relapsing after 18 months overall	31	24
Relapsing of patients with isolated small bowel disease (retrospective analysis)	40	22

*Trial of 55 children, mean age 13. All received prednisone to achieve remission; control group did not get 6-mercaptopurine.
†Trial of 76 patients, 40 receiving 15 mg methotrexate intramuscularly weekly, 36 receiving placebo.
‡Trial of 318 patients receiving 4 g/day of controlled-release mesalamine (Pentasa®) or placebo after intestinal resection.

study. This can likely be explained by the different entry criteria, with the children being newly diagnosed and steroid-"naïve" whereas in the "adult" trial many patients had previously been treated with steroids or had undergone surgical resections.

These trials offer additional confidence and reassurance regarding the "moderate-term" (ie 1-2 year) use of these agents, although we still need to define optimal means of dosing and determining the length of treatment from both safety and efficacy standpoints.

The paper by Feagan et al[11] offers support for the longer-term use of methotrexate for patients who have responded on a short-term basis. Methotrexate has become the standard immunomodulator for the treatment of rheumatoid arthritis. It is intriguing that the doses and requisite for parenteral administration are different in Crohn's disease.[10] Nevertheless, despite significant debate, methotrexate has not been generally accepted due to the lack of long-term data.[11] The current trial by Feagan as well as recently reported case series from France[12] and Chicago[13] demonstrate both controlled and observational benefits from continuing methotrexate for responsive patients.

The questions of which mesalamine formulation and dose is optimal, and which patient population is most likely to respond, remain open.

Two features do give grounds for concern regarding the composite data from these reports. The first is that the initial response to methotrexate compared to placebo for steroid-sparing was not as prominent as one might have hoped (43% vs 19%).[14] The second is that the response after one year, in our series from Chicago, declined at a faster rate. Ultimately, similar to the experience with the purine analogues, we will need to define the optimal dose and duration of therapy and, hopefully, be able to define the subgroups of patients who will respond to either agent.

The post-operative maintenance trial by Lochs et al is the largest such trial to be undertaken. Unfortunately, the results still do not reveal the ultimate role for mesalamine after surgical resections. The meta-analysis by Camma et al suggested that the efficacy of mesalamine maintenance therapy was more clearly defined in the post-operative setting than after induction of medical remissions.[5] However, the analysis was not able to determine an optimal mesalamine dose or delivery system, disease location, or inflammatory sub-type to improve response. The current trial utilized the highest dose to date and a delivery system that should have provided mesalamine independent of disease location. It still required a post-hoc analysis to identify a potential sub-group (limited small bowel disease) with an overall beneficial response. Some clinical investigators are questioning the role for mesalamine in maintenance of remission in Crohn's disease.[15] Still, a number of well-designed and well-controlled trials have demonstrated benefits in post-operative settings. The questions of which mesalamine formulation and dose is optimal, and which patient population is most likely to respond, remain open.

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NSAIDs

Gastrointestinal Safety of COX-2 Selective NSAIDs

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@article{Abecassis2000ConsensusSO, title={Consensus statement on the live organ donor.}, author={M. Abecassis and M. Adams and P. Adams and R. Arnold and C. Atkins and M. Barr and W. Bennett and M. Bia and D. Briscoe and J. Burdick and R. Corry and J. Davis and F. Delmonico and R. Gaston and W. Harmon and C. Jacobs and. J. Kahn and A. Leichtman and C. Miller and D. Moss and J. Newmann and L. S. Rosen and L. Siminoff and A. Spital and V. Starnes and C. Thomas and L. S. Tyler and L. Williams and F. Wright and S. Youngner}, journal={JAMA}, year={2000}, volume={284 22}, pages={. 2919-26 } }. M. Abecassis, M. Adams, +27 authors S. Youngner. Published 2000. Medicine. JAMA. Authors, Members of the Live Organ Donor Consensus Group, and Affiliations are listed at the end of this article. Objective To recommend practice guidelines for transplant physicians, primary care providers, health care planners, and all those who are concerned about the well-being of the live organ donor.Â The statement identifies issues of controversy; however, the wording of the entire statement is a consensus by approval of all attendees. Conclusion The person who gives consent to be a live organ donor should be competent, willing to donate, free of coercion, medically and psychosocially suitable, fully informed of the risks and benefits as a donor, and fully informed of the risks, benefits, and alternative treatment available to the recipient. The statement identifies issues of controversy; however, the wording of the entire statement is a consensus by approval of all attendees. Conclusion: The person who gives consent to be a live organ donor should be competent, willing to donate, free from coercion, medically and psychosocially suitable, fully informed of the risks and benefits as a donor, and fully informed of the risks, benefits, and alternative treatment available to the recipient. The benefits to both donor and recipient must outweigh the risks associated with the donation and transplantation of the living donor organ. Publication types. Consensus Development Conference. Research Support, Non-U.S. Gov't. The organ donation process involves a specialist team who ensure that donors are treated with the greatest care and respect during the removal of organs and tissue for donation. The retrieval of organs takes place in a normal operating theatre under sterile conditions, and is carried out by specialist surgeons. Afterwards the surgical incision is carefully closed and covered by a dressing in the normal way.Â Organ donation is a precious gift that saves lives. Transplant laws in the UK expressly prohibit the sale of human organs or tissue. The opt out system. The decision is still yours to make.Â Unless you record your decision on the NHS Organ Donor Register, we will not hold any details about you or your preferences. What withdrawal means in an opt out system. plantation of the living donor organ. The consensus statement will re-. view each of the components of this. premise as developed at the national.Â Transplant centerâ˜specific statistics of donor and recipient outcomes. Consensus statement on live organ donors. 2920 JAMA, December 13, 2000â€”Vol 284, No. 22 (Reprinted) Â©2000 American Medical Association. All rights reserved.