

Current questions in the treatment of childhood SLE.

There are three key issues for those who care for children with SLE.

The first is early identification of those children who have 'high risk' disease. Appropriate selection of those likely to do poorly if not aggressively treated with immunosuppressive therapy is essential if we are to obtain the best quality of life for the largest number. The second issue is maximization of the immunosuppressive therapy. We must give those who need immunosuppressive therapy enough to minimize the risk of recurrence while simultaneously balancing the risk of therapy related toxicity. The third issue is treatment of those who fail initial immunosuppressive therapy. What can we do for those children? Is there a regimen with an acceptable ratio of efficacy to toxicity? Further, we must ask ourselves what is acceptable toxicity in this situation?

You will not find the answers to these questions in any text. Nor will you find uniform agreement among those who treat children or adults with SLE. However, a simple, well-considered approach with a clear understanding of the questions, which must be answered, quickly resolves many of the 'dilemmas' broached in clinical discussions of individual patients on rounds, in clinics, and on bulletin boards.

Most recognize that the child with class IV DPGN and a creatinine of 2.0 mg/dl is already in trouble. However, serial renal biopsy studies clearly indicate that many adults with a relatively low chronicity index progress to renal failure despite treatment [1,2]. We cannot wait until the patient is obviously in trouble to begin therapy. Too often we are like the careless mother at the scenic overlook. There is a guardrail and two feet beyond it is a steep cliff dropping off to rocks hundreds of feet below. Little Johnny is playing on the railing, but he's still two feet short of the cliff. Now little Johnny is on the other side of the railing, but he's still a foot and a half from the edge. Now Johnny's looking down over the edge, but he's still a foot back. Why did those silly engineers put the fence two feet back and make it hard for people to look over the edge? Now Johnny's trying to get just a little closer to look at the rocks at the bottom. Now Johnny's – Oh my gosh!!!! How did that happen? What a tragedy!! Well of course if we'd known that was going to happen we

would have kept Johnny on this side of the guardrail, but it looked like he was still so far from the edge. All of us would be sympathetic to Johnny's mother for her loss, but all would say she was foolish to let Johnny climb over the guardrail. Do you initiate immunosuppressive therapy as soon as you see someone headed near the edge? How close do you let them get? Are you waiting till they are already over the edge? Faulting therapy for its inability to catch people once they've fallen is like saying the designers of the scenic overlook should have put netting on the side of the cliff to catch anyone who fell. Our emphasis must be on keeping everyone away from the edge. It is true that every Johnny doesn't fall, but does that make it safe to go past the guardrail?

In deciding where the 'edge' is we must balance probability of disease progression, if left untreated, versus efficacy of treatment and probability of toxicity from treatment. Each of these issues remains controversial. Again you won't find answers in books. From the perspective of twenty-five plus years experience, the simplest answer is the most informative. Children with recurrent lupus-related problems (e.g. infections, neurologic complications, hypertension, pulmonary hemorrhage, nephritis/nephrotic syndrome) do poorly over the long term if not aggressively treated. Not only do the problems keep recurring, but also with recurrent use of moderate to high dose corticosteroids to control these problems, steroid toxicity becomes a major issue. You do not need class IV DPGN, or a creatinine greater than 2.0 mg/dl, or in fact any nephritis at all to recognize the child at high risk. You simply need to recognize the child who is recurrently having problems that force you to raise the steroids above 0.5 mg/kg/day.

The breadth of the current recommendations for when to initiate IV cyclophosphamide is quite wide. The most aggressive would be my recommendation that any child with recurrent hypocomplementemia that you are unable to maintain satisfactorily on less than 0.5 mg/kg/day (I use 20 mg/day as the cutoff for 'normal sized' patients), should be given immunosuppressive therapy. The least aggressive is that IV cyclophosphamide is rarely indicated, but most investigators agree it is appropriate for anyone with biopsy proven DPGN. Some may be tempted to disagree with this recommendation. However the cumulative toxicity of recurrent use of high dose steroid usage on a growing child is often

not obvious until many years later. Over a five-year horizon children will generally do well without aggressive therapy, but in the five to ten year gap there is a dramatic separation between the children I have treated with IV cyclophosphamide and minimal steroids and the children who have chosen to be treated with steroids alone. A typical child who received IV cyclophosphamide reports, 'I only remember I have lupus when I come to the hospital for my checkups.' Similar results have been reported in studies of adults with lupus [3].

There are many who would respond to my suggestions by asking for 'evidence based medicine.' It's easy to ask. But in fact all of us are asked to make judgments without the evidence of long-term trials every day. Further, even if one assumed a large enough population of children with lupus was readily available for study and all would remain in the study for the fifteen years necessary to complete a prospective long term analysis, we wouldn't have satisfactory evidence based data for seventeen to twenty years. Yet, if every center agreed to start this study immediately, it is likely that cyclophosphamide would not be the optimal therapy under consideration by the time the study was completed. Knowing that over fifteen years a 1987 Dodge held up better than a 1987 Nissan is of only questionable value in buying a car in 2003. It will not be possible to appease those who want evidence based medicine regarding long-term outcome in children with chronic diseases without either having a time machine or committing ourselves to continuing a therapy long after a new and 'potentially superior' therapy has become available. Are there any of you who do not use etanercept because we don't know what will happen after twenty years? I don't expect any of you to shop for 1987 cars in 2003 because the long term data is in on which was better.

The major concern of most physicians is long-term toxicity of intravenous cyclophosphamide therapy. The answer is clear. In our long term experience at the Hospital for Special Surgery only one female (who received two full courses of therapy - 34 gms/M² of cyclophosphamide over 6 years) has developed amenorrhea. Extensive studies of children receiving intravenous cyclophosphamide for malignant conditions estimate the frequency of amenorrhea to range from a high of 16% in children receiving high dose chemotherapeutic regimens with irradiation to a low of 6% in children treated

with intravenous cyclophosphamide alone [4,5] Thus the risk of amenorrhea for children with SLE is probably 1/16 with the highest estimate being 1/6 [6]. The risk of death from SLE over ten years of follow-up in a similarly selected group of children for whom intravenous cyclophosphamide was avoided was 1/4. If one considers not only death, but failure to reproduce because of the cosmetic and psychological effects of chronic corticosteroids as well, the risk of 'reproductive failure' was far higher for those who avoided cyclophosphamide.

The risks of intravenous cyclophosphamide therapy are not limited to infertility. Additional risks include infection, hemorrhagic cystitis, and an increased incidence of late onset neoplastic diseases. With careful evaluation of the patient prior to cyclophosphamide administration and proper inpatient hydration and administration of MESNA our incidence of all these complications remains negligible in children who have received less than 20 gms/M² of cyclophosphamide. One child with long-term recalcitrant lupus who had received in excess of 60 gms/M² of intravenous cyclophosphamide developed a renal papillary cell carcinoma during his seventh year of therapy. However, as with amenorrhea there have been no neoplastic complications in children receiving the standard therapeutic regimen of 17 gms/M². Again this reflects the published adult data [7]

At every meeting I am asked about using less cyclophosphamide, using it for a shorter period, or waiting until the patient is doing very poorly to start. Often the question is followed by a complaint that their experience using cyclophosphamide in the past, has been poor. Their experience is poor because they use less cyclophosphamide, use it for a shorter period, or wait until the patient is doing very poorly. Even the best guardrail will not catch someone who has already fallen over the cliff.

The current regimen of intravenous cyclophosphamide is not the final answer. However, it clearly works well and with minimal toxicity. Our patients deserve the best shot at getting better and staying better. When I began in pediatric rheumatology the prognosis for ALL was far worse than for lupus. Now the prognosis for ALL is far better. The oncologists stick to their protocols. Do children with lupus deserve less?

There are reported abstracts and in a few cases manuscripts describing the use of mycophenolate mofetil, azathioprine, methotrexate, and cyclosporine in the treatment of children with lupus. None of these initial reports of these therapies has been followed by a report of continued efficacy. To date intravenous cyclophosphamide is the only therapy with long term follow-up data and repeated studies demonstrating consistent efficacy in a significant number of children. That doesn't mean intravenous cyclophosphamide is perfect. Only that at present it is the best we have.

Since 1983 I have treated more than fifty children with intravenous cyclophosphamide with SLE. The majority for whom follow-up is available are doing well on low dose prednisone without the stigmata of Cushing's syndrome. With long-term follow up it has become evident that not every child with lupus will respond completely to intravenous cyclophosphamide. Our recurrence rate is approximately 20%. Again this is similar to the published adult experience [8]. Most of these cases are children who flare within the first year of completing intravenous cyclophosphamide therapy. A few are children who flare during the initial course of intravenous cyclophosphamide therapy, usually when the frequency of cyclophosphamide administration changes from monthly to every three months. Since our two cases of significant toxicity (one amenorrhea and one renal carcinoma) occurred in children with recurrent disease who were continued on monthly intravenous cyclophosphamide it is clear this is not a satisfactory approach.

At the present time children with recurrent disease are treated with a nine-month course of monthly intravenous cyclophosphamide and monthly intravenous methotrexate (dose slowly increased from 50 mg/M² to 300 mg/M², given four hours after the intravenous cyclophosphamide). This dose of combine chemotherapy has brought continued active disease under control in all of the children so treated [9]. This regimen clearly causes more nausea and cytopenia than IV cyclophosphamide alone. It is also carries a higher risk of ultimate sterility and neoplasia. However, these are children with severe disease that has not remitted with intravenous cyclophosphamide alone. We continue to explore alternative therapies for this group.

For children who fail even this salvage therapy there is no 'standard' regimen. Bone marrow transplantation and IV cyclophosphamide marrow ablation without transplantation have both been utilized in adults and some teenagers [10]. The utility of these regimens remains unclear. Everyone who cares for children with SLE anxiously awaits a more effective and less toxic therapy than intravenous cyclophosphamide. However, until one is demonstrated, I am committed to giving the children in my care the best possible chance of long-term disease remission without significant corticosteroid toxicity. At present intravenous cyclophosphamide remains the only therapy proven to achieve that goal consistently.

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