

# The history of pulse therapy in lupus nephritis (1976–2016)

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## ABSTRACT

Pulse therapy with methylprednisolone became standard of care for the treatment of worsening lupus nephritis since its introduction in 1976. Even today, 40 years since its introduction, it is still a gold standard for this clinical condition. In this communication, we have reviewed the events that surrounded the use of this therapy by one of the authors of the original paper published in *Lancet* 40 years ago.

Glucocorticoids have been used for the management of inflammatory diseases for the last 60 years. The oral route is usually preferred for administration, with the minimum dose required to keep the disease state in remission. High-dose intravenous corticosteroids were initiated to successfully prevent renal allograft rejection.<sup>1–2</sup> I remember that Edgar Cathcart and I were talking with two nephrologists at the cafeteria of the University Hospital (Boston University) back in 1974 on the results with pulse therapy in allograft rejection and the idea came to try to abrogate acute deterioration of renal function in lupus patients with pulse therapy. The initial results of the first seven patients were published in January 1976.<sup>3</sup>

The initial experience was confirmed by other groups and was extended to other clinical manifestations of active lupus and autoimmune diseases requiring acute immunosuppression with extensive citation throughout the last 40 years (table 1). Since the publication of the original paper in 1976, bolus injections of steroids have suffered considerable variation in the dose, number, timing and duration of the higher dose. Despite 40 years of use, the clarity of the mechanism of action is still, to some extent, unknown. It is well known that pulse therapy is cumulatively less toxic than treatment with continuous oral steroids at lower doses. However, it is also known that pulse therapy may be associated with side effects and contraindicated in systemic infections and

uncontrolled hypertension and its use can lead to metabolic disturbances, and changes in behaviour, requiring adequate monitoring during its use (figures 1 and 2).

Ten years later, in 1986, the group at the National Institutes of Health reported the long-term results of their trial with monthly pulses of cyclophosphamide and later on, in further trials, confirmed the beneficial effects of high-dose steroids by combining pulses of cyclophosphamide with steroid pulses. It seems that, in the next decade, attempts to minimise steroid use in patients with systemic lupus erythematosus (SLE) and replacing it with B-cell depletion are starting to grow, but even in that scenario, in the beginning, patients will still receive limited number of pulse steroids, and in a just released paper, 69 SLE experts indicated their preferences to treat serious lupus nephritis and high-dose steroids are still the first line of treatment, followed by mycophenolate.<sup>4–8</sup>

**Table 1**

### Pubmed search 1976–2015

Lupus nephritis and pulse therapy	366 papers
Lupus disease and pulse therapy	1191 papers
Autoimmune disease and pulse therapy	4708 papers

*Lancet*. 1976 Jan 24;1(7952):163–6.

Beneficial effects of methylprednisolone "pulse" therapy in diffuse proliferative lupus nephritis.

Cathcart ES, Idelson BA, Scheinberg MA, Couser WG.

#### Abstract

Seven patients with diffuse proliferative lupus nephritis were subjected to high-dose intravenous methylprednisolone (pulse) therapy. Following the pulse, five patients with rapidly deteriorating renal function improved within three days and their serum-creatinine levels returned to baseline by one month. All seven patients demonstrated reversal of severe immunological abnormalities including increased serum D.N.A. binding, decreased serum C3 levels, and reduced number of T lymphocytes in the peripheral blood. This form of therapy may make it possible to maintain patients with lupus nephritis on lower doses of steroids than is normally feasible.

**Figure 1** Publication of the first paper on systemic lupus erythematosus nephritis.



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**Figure 2** Boston University team rheumatology section 1976 —MS on the left and Edgar Cathcart on the right.



**Contributors** We believe recalling the introduction of this therapy in lupus patients is of interest to the readers of Lupus Science and Medicine.

**Competing interests** None declared.

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