

# Impact of National List of Essential Medicines (NLEM) on Cost Variation of Immunosuppressants available in Indian Market

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## ABSTRACT

**Background:** Immunosuppressants are used commonly in two conditions: to prevent graft versus host rejection in transplantation and autoimmune disorders. Autoimmune diseases are chronic in nature requiring lifelong treatment. Organ transplantation is also expensive. Therefore, affordability of these medicines is crucial. To address the problem of affordability, government caps the prices of drugs included in National List of Essential Medicines. However, even cost variation among various brands of the drugs included in essential medicine list is of concern as majority of prescriptions are written using brand names. Hence this study was undertaken to evaluate impact of essential medicine list on cost variation of these drugs. **Materials and Methods:** Immunosuppressant drugs were broadly classified into two categories – drugs listed under National List of Essential Medicines and drugs not included. Prices of the drugs belonging to both the groups were obtained from website “Pharma Sahi Dam”. Later, cost ratio, percentage cost variation was calculated. The multiple linear regression analysis was performed to investigate association between percentage cost variation and essentiality/number of brands. **Results:** Immunosuppressant drugs showed wide cost variation. Overall higher cost

variation was seen among drugs not included in essential medicine list. This was further substantiated by multiple regression analysis ( $\beta = 0.316$ ,  $p = 0.021$ ). However, number of brands had no effect on cost variation.

**Conclusion:** Hence, to improve affordability of these drugs which are mainstay in autoimmune disorders and organ transplantation, regulatory bodies should widen the inclusion criteria for essential medicine list. Also, efforts are needed to create awareness of cost variation among prescribers.

**Keywords:** Immunosuppressants, Essential drugs, Economics, Cost analysis, Pharmacoeconomic.

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## INTRODUCTION

Immunosuppressant are drugs which inhibit cellular/humoral or both types of immune responses.<sup>1</sup> These drugs can be classified based on their mechanism of action and their synthesis into five broad groups – Calcineurin inhibitors, mechanistic target of rapamycin (m-TOR) inhibitors, antiproliferative drugs, glucocorticoids and biologic agents.<sup>1,2</sup>

Immunosuppressants are used commonly in two conditions: to prevent graft versus host rejection in transplantation and autoimmune disorders. Advent of immunosuppressants have made transplantation possible as a life saving measure in patients with failing organs. Until 1980s, primarily used immunosuppressants were azathioprine and glucocorticoids. In 1980s, discoveries of calcineurin inhibitors, tacrolimus and cyclosporine resulted in better graft outcomes.<sup>3</sup> Subsequently, development in recombinant deoxyribonucleic acid (DNA) technology and other advances in molecular biology led to the era of biological agents in the immunosuppression therapy.<sup>4</sup> Immunosuppressants are used in both solid organ transplantation and bone marrow transplantation. However, organ transplantation is costly, even in developed country like USA, long term oral maintenance immunosuppression and other prescription medications can cost patients upwards of \$2,500.00 per month.<sup>5</sup>

Immunosuppressants are used in autoimmune disorders like rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, multiple sclerosis, type I diabetes mellitus, psoriasis, grave's disease, myasthenia gravis.<sup>6,7</sup> These drugs are also used in chronic inflammatory demyelinating polyneuropathy, collagenous colitis, dermatomycosis,

pemphigus, polyarteritis nodosa, Reiter's syndrome, Schilder's Disease, scleritis, Sjogren's syndrome, sympathetic ophthalmitis, temporal arteritis, thrombocytopenia and other autoimmune conditions.<sup>6</sup> Incidences of autoimmune diseases are on rise in India in recent times.<sup>8</sup>

Commonly prescribed drugs in autoimmune diseases are disease modifying anti rheumatic drugs (DMARDs), glucocorticoids and non-steroidal anti-inflammatory drugs (NSAIDs). Anti-TNF-alpha inhibitors are also widely used.<sup>9</sup> Autoimmune diseases are chronic in nature mostly requiring lifelong treatment. Hence, these diseases result in huge amount of direct as well as indirect cost, and also high-out of pocket cost.<sup>10</sup> Therefore, affordability of these medicines is crucial.

In 2020, total government health expenditure was 1.8% of GDP in India, which is lower than other countries.<sup>11</sup> Because of this funding inadequacy, public health infrastructure suffers, impacting the rural segments the most.<sup>12</sup> Moreover, health insurance coverage is also low, resulting in huge out of pocket expenditure.<sup>13-14</sup>

To address the above problem, India has introduced policies since 1962, the policy began with the 'Drug (price control) order' (DPCO) of 1962. It was followed with series of orders in 1970, 1979, 1987 and 1995. In 1997, National Pharmaceutical Pricing Authority of India (NPPA) was established under Ministry of chemicals and Fertilizers. The NPPA implemented a national pharmaceuticals price policy and DPCOs to regulate the prices of scheduled and non-scheduled drugs. Currently, National Pharmaceuticals Pricing Policy through DPCO caps prices

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of the drugs which are deemed to be essential through National list of Essential Medicines. Presently, prices of 871 drugs listed in NLEM 2015 are capped. The ceiling price for a drug is the average of the prices of available brands with market share of at least 1%, and annual revision is allowed on the basis of the variations in the Wholesale Price Index. However, NPPA caps or fixes ceiling price for the formulation of particular strength which does not guarantee reduced cost variation among various brands of the drug.<sup>15-16</sup>

Cost variation among various brands of the drug is crucial as majority of prescriptions are written using brand names,<sup>17-18</sup> even though MCI/NMC mandates physician to prescribe using generic names.<sup>19</sup> Further, prescribing costly drugs can lead to decrease in patient compliance, adversely affect physician-patient relationship and can have psychological impact on patients grappling with financial hardships.<sup>20-21</sup>

Hence this study was undertaken to analyze cost variation among different brands of commonly used immunosuppressant drugs in India. Another objective of the study was to analyze difference in cost variation among drug prices controlled by DPCO (Drugs in National list of essential medicines) and those which are not controlled (not in National list of Essential Medicines).

## MATERIALS AND METHODS

Immunosuppressant drugs were broadly classified into two categories- drugs listed under National List of Essential Medicines (NLEM)<sup>22</sup> and drugs not included (NNLEM), but used as immunosuppressants. Fixed dose combination was excluded from the study. Prices of the drugs belonging to both the groups were obtained from website "Pharma Sahi Dam" (<https://nppaimis.nic.in> / [nppaprice.pharmasahidaamweb](https://nppaprice.pharmasahidaamweb)).

Pharma Sahi Dam is developed and maintained by "National Pharmaceutical Pricing Authority" which is a credible online search tool to check prices of scheduled/non-scheduled drugs. Unit prices of all available brands for given formulation of each drug were recorded. The drug strength was considered only if it was available from two or more manufacturers.

*Ceiling price of the NLEM drugs was noted. Other parameters recorded were the minimum and maximum cost per unit in Rupees (INR) of a particular drug formulation. Later, cost ratio was calculated, it is the ratio of the cost of the costliest to cheapest brand of the same drug. Furthermore, % cost variation was calculated using following formula.*

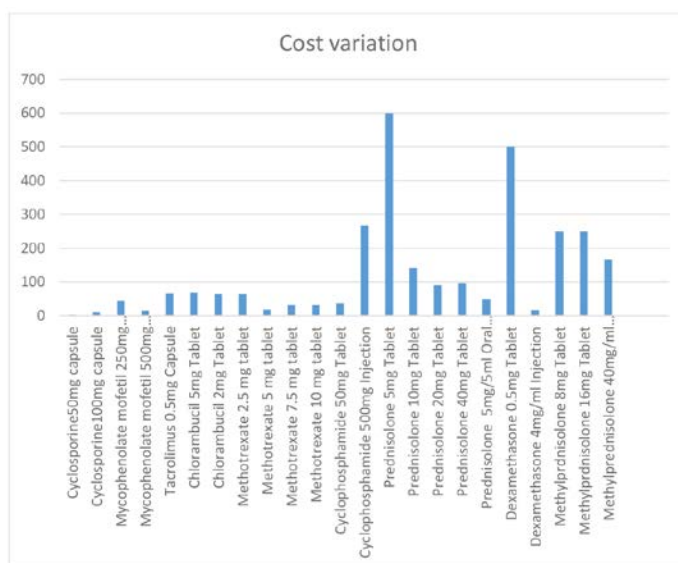
$$\% \text{ cost variation} = \frac{\text{Maximum cost} - \text{minimum cost}}{\text{Minimum cost}} \times 100$$

The multiple linear regression analysis was performed to investigate association between % cost variation and study independent variables such as essentiality and number of brands. This was performed using IBM SPSS software.

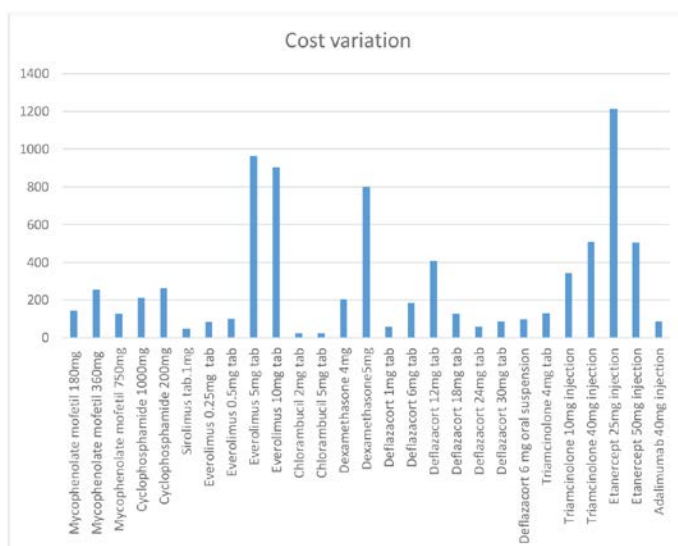
## RESULTS

NLEM group had 9 drugs (23 different strengths/doses) while NNLEM had 10 drugs (27 different strengths/doses). Figure 1 and 2 bar diagrams depict cost variation among drugs from NLEM group and NNLEM respectively.

Immunosuppressant drugs showed wide cost variation. Maximum % cost variation among drugs NLEM drugs was seen with prednisolone 5mg tablet (600%) and dexamethasone 0.5mg tablet (500%), however cost of per tablet is very low that is about in range of INR. 0.1-0.7 and INR. 0.1-0.6 respectively, and hence practically %cost variation is insignificant. Minimum cost variation is seen 2% with cyclosporine 50 mg capsule.



**Figure 1:** Bar diagram showing cost variation among various drugs from NLEM group.



**Figure 2:** Bar diagram showing cost variation among various drugs from NNLEM group.

Another drug from NLEM group - Cyclophosphamide injection (200mg) also showed high % cost variation that is about 267%. Minimum cost per unit was found to be INR 16 whereas maximum cost was INR 60. Cost variation was seen across all strengths of methylprednisolone, however highest was seen in case of methylprednisolone tablet (8mg, 16mg) that is 250%.

Among NNLEM group, maximum cost variation of 1213% was seen in case of Etanercept 25 mg injection. Everolimus 5mg and 10 mg tablet showed huge cost variation of greater than 900%. Triamcinolone 10mg, 40mg injection, etanercept injection 50 mg, deflazacort 12mg tablet showed 342%, 508%, 505%, 409% of cost variation respectively.

Overall higher cost variation was seen in NNLEM drugs. This was further substantiated by multiple regression analysis (Table 1).  $\beta = 0.316$ ,  $p = 0.021$ , (significant as  $p < 0.05$ ) proved that listing of drugs as essential medicines and ceiling their prices reduced cost variation among various

**Table 1: Multiple regression analysis summary of percentage cost variation (PCV).**

Factor	Unstandardized coefficient (B)	S.E (B)	Standardized Coefficient (β)	t	Significance
Constant	-55.223	118.879		-.465	.644
Essentiality	165.463	69.422	.316	2.383	.021
No. of brands	1.184	6.101	.026	.194	.847

brands. However, number of brands had no effect on cost variation ( $\beta = 0.026$ ,  $p = 0.847$ ).

## DISCUSSION

As we know, immunosuppressants are used in wide range of conditions. Most crucial being their role in organ transplantation and autoimmune disorders. In both these conditions drugs are required to be taken for long time often lifelong. Hence affordability of these drugs is important.

To regulate prices of the drug, National Pricing Authority of India caps the prices of drugs listed in National List of Essential Medicines. NPPA regulates prices by implementing Market Based Price (MBP) strategy. This strategy is based on current market prices of a drug formulation of therapeutic class and market data. In case, if there are many drugs in particular category, this method takes simple average of all prices of all drugs that have 1% market share plus 16% Pharmacists margin. However, if drug is the only one in the category, price ceiling will be fixed percent, based on price reductions in similar category.<sup>15,23-24</sup>

National list of essential medicines termed as best fit. As, it is based on efficacy, safety, major public health problems of India and cost-effectiveness. Our study also supported claims of NPPA and found that inclusion of drugs into national list of essential medicines reduced percentage cost variation among brands ( $\beta = 0.316$ ,  $p = 0.021$ ). Few studies were carried out previously to decipher impact of NLEM on cost variations. However, all those studies involved other groups of drugs and not immunosuppressants. Findings of one such study on CVS drugs revealed that inclusion of drugs in National List of Essential Medicine had no impact on their cost variation.<sup>25</sup> Another study conducted on neuropsychiatric drugs found that NLEM drugs were economical than NNLEM in case of antiepileptic, antidepressant, and drugs for bipolar disorder. However as per same study, antimigraine drugs and drugs for generalized anxiety disorders, NNLEM drugs were more economical.<sup>26</sup> Study by Meena *et al.* on antibiotics listed in NLEM, found wide range of cost variation among drugs. However this study did not compare its result with NNLEM.<sup>27</sup>

This study findings revealed that higher cost variation was seen with drugs listed in NNLEM. Hence inclusion of a greater number of drugs into the National List of Essential Medicines will lead to decreased cost variation and better affordability. Another concern is selective inclusion of certain formulations of drugs into NLEM and not others. Hence for efficient regulation of prices, all the formulations of particular drug should be included in National List of Essential Medicines.

Study results indicated that there is no association between number of brands and cost variation among various brands. Our findings were similar to study conducted by Ray *et al.* which also found weak correlation between number of brands and cost variation among drugs used in thromboembolic disorders.<sup>28</sup> However, another study involving CVS drugs found that cost variation is directly proportional to the

number of brands available in the market.<sup>25</sup> Hence, we can conclude that association between number of brands and cost variation may be therapeutic class specific and larger pharmacoeconomic analyses are required to get a broader perspective.

Furthermore, with drugs used in organ transplantation, switching brands can lead to over suppression or under suppression of immune function due to varying equivalence criteria to demonstrate bioequivalence between innovator and generic drugs.<sup>29</sup> Thus mandating physician to prescribe by generic name of the drug can lead to serious consequences. Hence, before mandating generic name prescriptions, there is a need of more specific BA/BE study guidelines for more reliable generic drugs.

Previous studies have also revealed that physician's lack of knowledge about cost of drug and cost variation among various brands.<sup>30</sup> Hence, focus should be to improve the knowledge as well as their access to cost information.

Our study had few limitations. One being only drug formulations whose prices for at least two brands were available on Pharma Sahi Dam were considered. Another limitation being certain formulation prices were not at all available, hence those were not included in the study.

## CONCLUSION

Wide range of cost variation was observed among various immunosuppressant drugs available in Indian Market. Our study also revealed that inclusion of drugs in National List of Essential Medicine reduces its cost variation. Hence to improve affordability of these drugs which are mainstay in autoimmune disorders and organ transplantation, regulatory bodies should widen the inclusion criteria of NLEM. Thus, increasing number of NLEM drugs. Furthermore, laying of stringent guidelines for BA/BE studies is required in order to have reliable generic drugs, so physician can prescribe using generic name without having serious health consequences. Also, efforts are needed to create awareness of cost variation among prescribers.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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