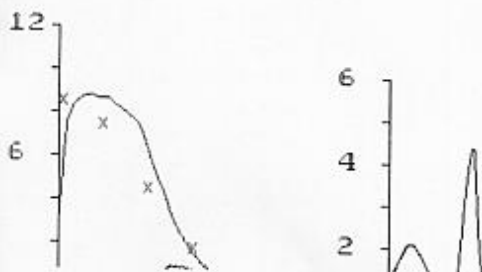


|             |     | oss.   | teorici | %   | lim.      |
|-------------|-----|--------|---------|-----|-----------|
| VC          | l   | 4.76   | 4.52    | 105 | 3.60-5.44 |
| IVC         | l   | 4.68   | 4.52    | 103 | 3.60-5.44 |
| FVC         | l   | 4.42   | 4.34    | 102 | 3.34-5.34 |
| FEV1        | l   | 3.69   | 3.44    | 107 | 2.60-4.28 |
| FEV1/VC     | %   | 77.45  | 76.83   | 101 | 65.0-88.6 |
| FEV1/FVC    | %   | 83.48  |         |     |           |
| RV          | l   | 2.23   | 2.36    | 94  | 1.69-3.03 |
| FRC         | l   | 2.82   | 3.65    | 77  | 2.66-4.64 |
| TLC         | l   | 6.99   | 7.06    | 99  | 5.91-8.21 |
| RV/TLC      | %   | 31.86  | 36.21   | 88  | 27.2-45.2 |
| FRC/TLC     | %   | 40.32  | 56.00   | 72  | 44.9-67.1 |
| PEF         | l/s | 8.83   | 8.54    | 103 | 6.5-10.5  |
| MEF75       | l/s | 8.68   | 7.51    | 116 | 4.7-10.3  |
| MEF50       | l/s | 6.45   | 4.57    | 141 | 2.40-6.74 |
| MEF25       | l/s | 1.44   | 1.77    | 81  | 0.49-3.05 |
| FIVC        | l   | 3.94   |         |     |           |
| FIV1        | l   | 3.90   |         |     |           |
| PIF         | l/s | 5.29   |         |     |           |
| MIF50       | l/s | 5.29   |         |     |           |
| FEV1/FIV1   | %   | 94.62  |         |     |           |
| FEF25-75    | l/s | 4.30   | 3.65    | 118 | 1.94-5.36 |
| MEF50/MIF50 | %   | 121.91 |         |     |           |

Teorici di Riferimento: Polgar 71 (6<eta'<18) ERS93 (18<=eta')

il Medico



|             |     | oss.  | teorici | %   | lim.      | post-br | %/oss. |
|-------------|-----|-------|---------|-----|-----------|---------|--------|
| VC          | l   | 4.58  | 4.50    | 102 | 3.58-5.42 | 4.72    | 103    |
| IVC         | l   | 4.58  | 4.50    | 102 | 3.58-5.42 |         |        |
| FVC         | l   | 4.37  | 4.31    | 101 | 3.31-5.31 | 4.72    | 108    |
| FEV1        | l   | 2.63  | 3.62    | 73  | 2.78-4.46 | 3.01    | 114    |
| FEV1/VC     | %   | 57.45 | 80.59   | 71  | 68.8-92.4 | 63.82   | 111    |
| FEV1/FVC    | %   | 60.19 |         |     |           | 63.82   | 106    |
| RV          | l   | 1.48  | 1.77    | 84  | 1.10-2.44 |         |        |
| FRC         | l   | 2.21  | 3.22    | 69  | 2.23-4.21 |         |        |
| TLC         | l   | 6.06  | 6.27    | 97  | 5.12-7.42 |         |        |
| RV/TLC      | %   | 24.44 | 28.08   | 87  | 19.1-37.1 |         |        |
| FRC/TLC     | %   | 36.51 | 51.59   | 71  | 40.5-62.7 |         |        |
| PEF         | l/s | 7.23  | 8.83    | 82  | 6.8-10.8  | 8.31    | 115    |
| MEF75       | l/s | 2.95  | 7.57    | 39  | 4.8-10.4  | 4.00    | 136    |
| MEF50       | l/s | 1.74  | 4.84    | 36  | 2.67-7.01 | 2.33    | 134    |
| MEF25       | l/s | 0.64  | 2.05    | 31  | 0.77-3.33 | 1.09    | 170    |
| FIVC        | l   | 4.04  |         |     |           | 4.06    | 101    |
| FIV1        | l   | 4.02  |         |     |           | 4.02    | 100    |
| PIF         | l/s | 8.09  |         |     |           | 6.31    | 78     |
| MIF50       | l/s | 7.89  |         |     |           | 5.84    | 74     |
| FEV1/FIV1   | %   | 65.37 |         |     |           | 74.95   | 115    |
| FEF25-75    | l/s | 1.42  | 4.35    | 33  | 2.64-6.06 | 2.15    | 151    |
| MEF50/MIF50 | %   | 22.06 |         |     |           | 39.84   | 181    |

Teorici di Riferimento: Polgar 71 (6<eta'<18) ERS93 (18<=eta')

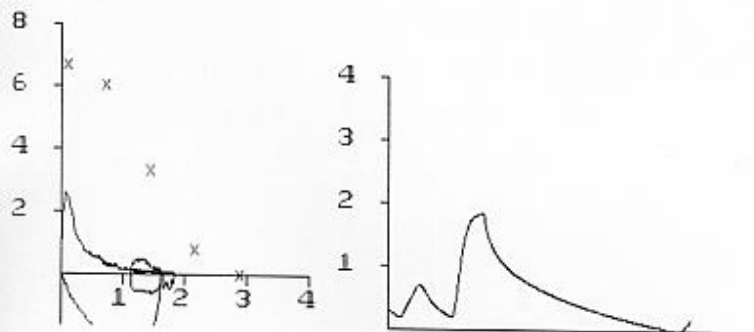
il Medico



|             |     | oss.  | teorici | %   | lim.       | post-br | %/oss. |
|-------------|-----|-------|---------|-----|------------|---------|--------|
| VC          | l   | 2.24  | 2.99    | 75  | 2.07-3.91  | 1.91    | 85     |
| ERV         | l   | 0.72  |         |     |            |         |        |
| FVC         | l   | 1.84  | 2.90    | 64  | 1.90-3.90  | 1.66    | 90     |
| FEV1        | l   | 0.78  | 2.17    | 36  | 1.33-3.01  | 0.75    | 97     |
| FEV1/VC     | %   | 34.68 | 73.25   | 47  | 61.4-85.0  | 39.37   | 114    |
| FEV1/FVC    | %   | 42.09 |         |     |            | 45.20   | 107    |
| RV          | l   | 1.67  | 2.59    | 64  | 1.92-3.26  |         |        |
| FRC         | l   | 2.44  | 3.45    | 71  | 2.46-4.44  |         |        |
| TLC         | l   | 3.90  | 5.79    | 67  | 4.64-6.94  |         |        |
| RV/TLC      | %   | 42.72 | 43.95   | 97  | 34.9-52.9  |         |        |
| FRC/TLC     | %   | 62.39 | 60.20   | 104 | 49.1-71.3  |         |        |
| PEF         | l/s | 2.63  | 6.70    | 39  | 4.71-8.69  | 2.27    | 86     |
| MEF75       | l/s | 0.68  | 6.06    | 11  | 3.25-8.87  | 0.67    | 99     |
| MEF50       | l/s | 0.27  | 3.34    | 8   | 1.17-5.51  | 0.27    | 100    |
| MEF25       | l/s | 0.14  | 0.83    | 17  | -0.45-2.11 | 0.08    | 58     |
| FIVC        | l   | 1.63  |         |     |            | 1.91    | 117    |
| FIV1        | l   | 1.56  |         |     |            | 1.80    | 115    |
| PIF         | l/s | 2.35  |         |     |            | 2.54    | 108    |
| MIF50       | l/s | 2.16  |         |     |            | 2.54    | 117    |
| FEV1/FIV1   | %   | 49.64 |         |     |            | 41.83   | 84     |
| FEF25-75    | l/s | 0.22  | 2.47    | 9   | 0.76-4.18  | 0.21    | 97     |
| MEF50/MIF50 | %   | 12.50 |         |     |            | 10.65   | 85     |

Teorici di Riferimento: Polgar 71 (6<eta'<18) ERS93 (18<=eta')

il Medico



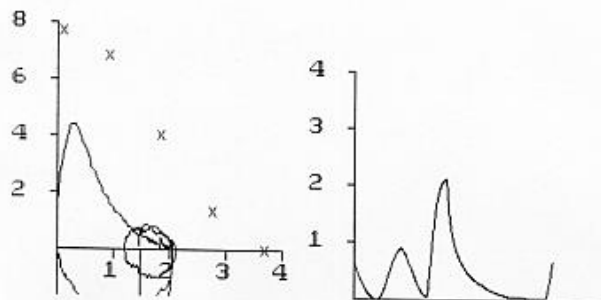
data: 24/11/2006

cartella n: 13277

|             |     | oss.  | teorici | %   | lim.      | post-br | %/oss. |
|-------------|-----|-------|---------|-----|-----------|---------|--------|
| VC          | l   | 2.47  | 3.84    | 64  | 2.92-4.76 | 2.08    | 84     |
| IVC         | l   | 2.40  | 3.84    | 63  | 2.92-4.76 |         |        |
| FVC         | l   | 2.07  | 3.69    | 56  | 2.69-4.69 | 1.94    | 94     |
| FEV1        | l   | 1.54  | 2.89    | 53  | 2.05-3.73 | 1.36    | 88     |
| FEV1/VC     | %   | 62.37 | 75.57   | 83  | 63.8-87.4 | 65.18   | 105    |
| FEV1/FVC    | %   | 74.40 |         |     |           | 69.96   | 94     |
| RV          | l   | 3.14  | 2.41    | 130 | 1.74-3.08 |         |        |
| FRC         | l   | 3.58  | 3.52    | 102 | 2.53-4.51 |         |        |
| TLC         | l   | 5.61  | 6.43    | 87  | 5.28-7.58 |         |        |
| RV/TLC      | %   | 55.95 | 38.92   | 144 | 29.9-47.9 |         |        |
| FRC/TLC     | %   | 63.88 | 57.47   | 111 | 46.4-68.6 |         |        |
| PEF         | l/s | 4.45  | 7.75    | 57  | 5.76-9.74 | 4.69    | 105    |
| MEF75       | l/s | 3.55  | 6.87    | 52  | 4.06-9.68 | 3.11    | 88     |
| MEF50       | l/s | 1.41  | 4.04    | 35  | 1.87-6.21 | 1.00    | 71     |
| MEF25       | l/s | 0.45  | 1.38    | 33  | 0.10-2.66 | 0.17    | 38     |
| FIVC        | l   | 2.17  |         |     |           | 2.08    | 96     |
| FIV1        | l   | 2.17  |         |     |           | 1.98    | 91     |
| PIF         | l/s | 3.64  |         |     |           | 3.54    | 97     |
| MIF50       | l/s | 3.58  |         |     |           | 2.45    | 68     |
| FEV1/FIV1   | %   | 70.94 |         |     |           | 68.46   | 97     |
| PEF25-75    | l/s | 1.14  | 3.19    | 36  | 1.48-4.90 | 0.65    | 57     |
| MEF50/MIF50 | %   | 39.24 |         |     |           | 40.74   | 104    |

Teorici di Riferimento: Polgar 71 (6<eta'<18) ERS93 (18<=eta')

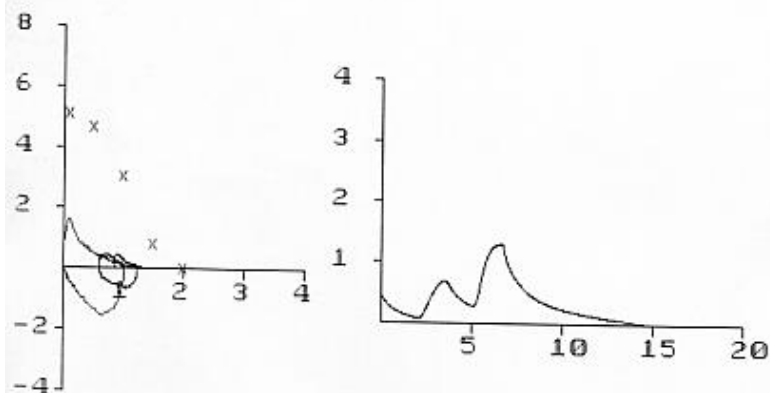
il Medico



|          |     | oss.  | teorici | %   | lim.       | post-br | %/oss. |
|----------|-----|-------|---------|-----|------------|---------|--------|
| VC       | l   | 1.33  | 1.97    | 68  | 1.28-2.66  | 1.25    | 94     |
| IVC      | l   | 1.33  | 2.12    | 63  | 1.43-2.81  |         |        |
| FVC      | l   | 1.31  | 2.00    | 66  | 1.29-2.71  | 1.25    | 96     |
| FEV1     | l   | 0.69  | 1.62    | 42  | 1.00-2.24  | 0.71    | 103    |
| FEV1/VC  | %   | 51.85 | 74.51   | 70  | 63.8-85.2  | 56.60   | 109    |
| FEV1/FVC | %   | 52.51 |         |     |            | 56.60   | 108    |
| RV       | l   | 2.42  | 2.02    | 120 | 1.44-2.60  |         |        |
| FRC      | l   | 2.54  | 2.55    | 99  | 1.73-3.37  |         |        |
| TLC      | l   | 3.75  | 4.44    | 84  | 3.45-5.43  |         |        |
| RV/TLC   | %   | 64.50 | 44.42   | 145 | 34.8-54.0  |         |        |
| FRC/TLC  | %   | 67.73 | 57.22   | 118 | 47.4-67.0  |         |        |
| PEF      | l/s | 1.62  | 5.14    | 31  | 3.66-6.62  | 1.81    | 112    |
| MEF75    | l/s | 0.82  | 4.68    | 18  | 2.46-6.90  | 0.85    | 104    |
| MEF50    | l/s | 0.36  | 3.05    | 12  | 1.24-4.86  | 0.36    | 100    |
| MEF25    | l/s | 0.14  | 0.83    | 16  | -0.30-1.96 | 0.08    | 56     |
| FEF25-75 | l/s | 0.30  | 2.28    | 13  | 0.88-3.68  | 0.30    | 99     |

Teorici di Riferimento: Polgar 71 ( $6 < \eta' < 18$ ) ERS93 ( $18 \leq \eta'$ )

il Medico



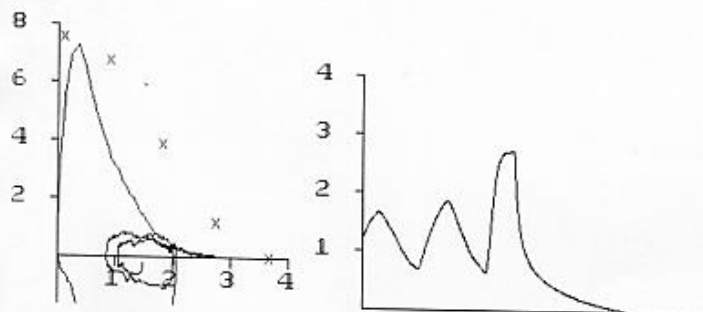
data: 27/11/2002

cartella n: 8266

|           |     | oss.  | teorici | %  | lim.       | post-br | %/oss. |
|-----------|-----|-------|---------|----|------------|---------|--------|
| VC        | l   | 3.01  | 3.80    | 79 | 2.88-4.72  | 2.91    | 96     |
| IVC       | l   | 2.94  | 3.80    | 77 | 2.88-4.72  |         |        |
| FVC       | l   | 2.73  | 3.66    | 74 | 2.66-4.66  | 2.91    | 106    |
| FEV1      | l   | 1.97  | 2.77    | 71 | 1.93-3.61  | 1.98    | 101    |
| FEV1/VC   | %   | 65.39 | 73.79   | 89 | 62.0-85.6  | 68.19   | 104    |
| FEV1/FVC  | %   | 72.16 |         |    |            | 68.19   | 94     |
| RV        | l   | 1.84  | 2.68    | 68 | 2.01-3.35  |         |        |
| FRC       | l   | 2.87  | 3.71    | 78 | 2.72-4.70  |         |        |
| TLC       | l   | 4.85  | 6.75    | 72 | 5.60-7.90  |         |        |
| RV/TLC    | %   | 37.89 | 42.78   | 89 | 33.8-51.8  |         |        |
| FRC/TLC   | %   | 59.25 | 59.57   | 99 | 48.5-70.7  |         |        |
| PEF       | l/s | 7.28  | 7.56    | 96 | 5.57-9.55  | 7.44    | 102    |
| MEF75     | l/s | 4.94  | 6.80    | 73 | 3.99-9.61  | 4.74    | 96     |
| MEF50     | l/s | 1.88  | 3.89    | 48 | 1.72-6.06  | 1.74    | 92     |
| MEF25     | l/s | 0.37  | 1.22    | 30 | -0.06-2.50 | 0.54    | 147    |
| FIVC      | l   |       |         |    |            | 2.29    |        |
| FIV1      | l   |       |         |    |            | 2.15    |        |
| PIF       | l/s |       |         |    |            | 3.15    |        |
| FEV1/FIV1 | %   |       |         |    |            | 92.18   |        |
| PEF25-75  | l/s | 1.28  | 2.84    | 45 | 1.13-4.55  | 1.33    | 104    |

Teorici di Riferimento: Polgar 71 (6<eta'<18) ERS93 (18<=eta')

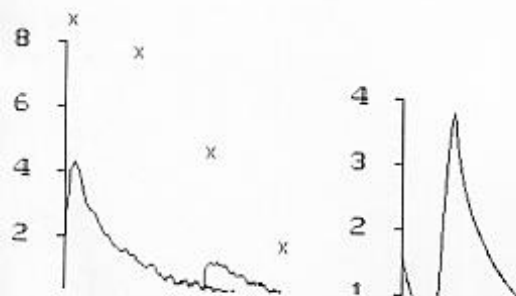
il Medico



|             |     | oss.  | teorici | %   | lim.      | post-br | %/oss. |
|-------------|-----|-------|---------|-----|-----------|---------|--------|
| VC          | l   | 4.99  | 4.78    | 104 | 3.86-5.70 | 4.56    | 91     |
| IVC         | l   | 4.99  | 4.78    | 104 | 3.86-5.70 |         |        |
| FVC         | l   | 3.80  | 4.58    | 83  | 3.58-5.58 | 4.56    | 120    |
| FEV1        | l   | 1.65  | 3.57    | 46  | 2.73-4.41 | 1.79    | 109    |
| FEV1/VC     | %   | 32.98 | 75.75   | 44  | 64.0-87.6 | 39.26   | 119    |
| FEV1/FVC    | %   | 43.32 |         |     |           | 39.29   | 91     |
| RV          | l   | 4.16  | 2.59    | 161 | 1.92-3.26 |         |        |
| FRC         | l   | 4.63  | 3.87    | 120 | 2.88-4.86 |         |        |
| TLC         | l   | 9.15  | 7.62    | 120 | 6.47-8.77 |         |        |
| RV/TLC      | %   | 45.43 | 38.53   | 118 | 29.5-47.5 |         |        |
| FRC/TLC     | %   | 50.65 | 57.26   | 88  | 46.2-68.4 |         |        |
| PEF         | l/s | 4.31  | 8.71    | 50  | 6.7-10.7  | 4.49    | 104    |
| MEF75       | l/s | 1.64  | 7.72    | 21  | 4.9-10.5  | 1.81    | 110    |
| MEF50       | l/s | 0.73  | 4.64    | 16  | 2.47-6.81 | 0.86    | 118    |
| MEF25       | l/s | 0.32  | 1.79    | 18  | 0.51-3.07 | 0.46    | 145    |
| FIVC        | l   | 3.40  |         |     |           | 4.56    | 134    |
| FIV1        | l   | 3.37  |         |     |           | 3.70    | 110    |
| PIF         | l/s | 4.63  |         |     |           | 3.63    | 78     |
| MIF50       | l/s | 4.40  |         |     |           | 3.63    | 83     |
| FEV1/FIV1   | %   | 48.80 |         |     |           | 48.37   | 99     |
| FEF25-75    | l/s | 0.62  | 3.52    | 18  | 1.81-5.23 | 0.75    | 122    |
| MEF50/MIF50 | %   | 16.64 |         |     |           | 23.70   | 142    |

Teorici di Riferimento: Polgar 71 (6<eta'<18) ERS93 (18<=eta')

il Medico



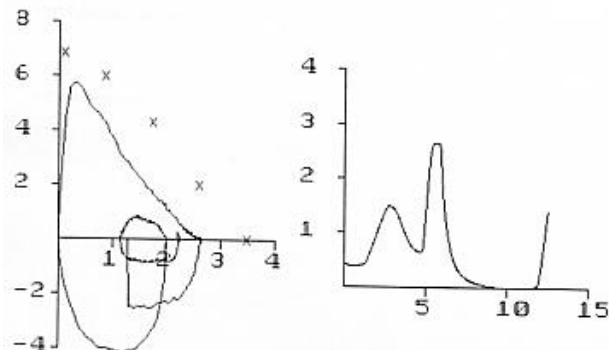
data: 19/04/2005

cartella n: 11275

|          |     | oss.  | teorici | %  | lim.      | post-br | %/oss. |
|----------|-----|-------|---------|----|-----------|---------|--------|
| VC       | l   | 2.86  | 3.47    | 83 | 2.78-4.16 | 2.87    | 100    |
| IVC      | l   | 2.86  | 3.53    | 81 | 2.84-4.22 |         |        |
| FVC      | l   | 2.67  | 3.48    | 77 | 2.77-4.19 | 2.87    | 107    |
| FEV1     | l   | 2.28  | 3.02    | 75 | 2.40-3.64 | 2.47    | 108    |
| FEV1/VC  | %   | 79.73 | 83.15   | 96 | 72.4-93.8 | 86.17   | 108    |
| FEV1/FVC | %   | 85.39 |         |    |           | 86.17   | 101    |
| RV       | l   | 0.96  | 1.43    | 67 | 0.85-2.01 |         |        |
| FRC      | l   | 1.71  | 2.66    | 64 | 1.84-3.48 |         |        |
| TLC      | l   | 3.82  | 4.90    | 78 | 3.91-5.89 |         |        |
| RV/TLC   | %   | 25.12 | 29.34   | 86 | 19.7-38.9 |         |        |
| FRC/TLC  | %   | 44.73 | 50.07   | 89 | 40.3-59.9 |         |        |
| PEF      | l/s | 5.80  | 6.88    | 84 | 5.40-8.36 | 5.88    | 101    |
| MEF75    | l/s | 4.77  | 6.03    | 79 | 3.81-8.25 | 5.32    | 111    |
| MEF50    | l/s | 2.85  | 4.35    | 66 | 2.54-6.16 | 3.71    | 130    |
| MEF25    | l/s | 1.33  | 2.03    | 65 | 0.90-3.16 | 1.68    | 126    |
| FEF25-75 | l/s | 2.48  | 3.90    | 64 | 2.50-5.30 | 3.17    | 128    |

Teorici di Riferimento: Polgar 71 (6<eta'<18) ERS93 (18<=eta')

il Medico





Nuove Cliniche III piano Via Rampari di S. Rocco 44100 Ferrara tel. 0532/:

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sesso: M d.n.: 02/10/19

g.e.: B

alt.: 168 eta': 63

peso: 76.0 c.r.:

tel.: 051/975059

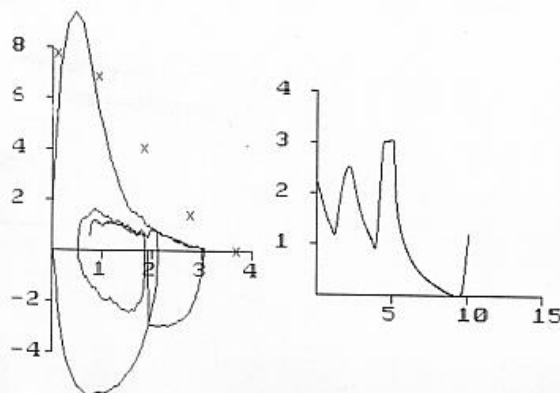
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data: 26/11/2002

cartella n: 8257

|          |     | oss.  | teorici | %   | lim.      | post-br | %/oss. |
|----------|-----|-------|---------|-----|-----------|---------|--------|
| VC       | l   | 3.07  | 3.84    | 80  | 2.92-4.76 | 3.03    | 99     |
| FVC      | l   | 3.05  | 3.69    | 83  | 2.69-4.69 | 3.03    | 99     |
| FEV1     | l   | 2.25  | 2.91    | 77  | 2.07-3.75 | 2.29    | 102    |
| FEV1/VC  | %   | 73.31 | 75.93   | 97  | 64.1-87.7 | 75.36   | 103    |
| FEV1/FVC | %   | 73.70 |         |     |           | 75.36   | 102    |
| RV       | l   | 1.93  | 2.35    | 82  | 1.68-3.02 |         |        |
| FRC      | l   | 3.04  | 3.48    | 87  | 2.49-4.47 |         |        |
| TLC      | l   | 5.00  | 6.35    | 79  | 5.20-7.50 |         |        |
| RV/TLC   | %   | 38.58 | 38.14   | 101 | 29.1-47.1 |         |        |
| FRC/TLC  | %   | 60.76 | 57.05   | 106 | 46.0-68.2 |         |        |
| PEF      | l/s | 9.40  | 7.77    | 121 | 5.78-9.76 | 8.90    | 95     |
| MEF75    | l/s | 7.48  | 6.87    | 109 | 4.06-9.68 | 7.59    | 101    |
| MEF50    | l/s | 1.75  | 4.07    | 43  | 1.90-6.24 | 1.89    | 108    |
| MEF25    | l/s | 0.63  | 1.40    | 45  | 0.12-2.68 | 0.63    | 100    |
| FEF25-75 | l/s | 1.59  | 3.26    | 49  | 1.55-4.97 | 1.70    | 107    |

Teorici di Riferimento: Polgar 71 (6<eta'<18) ERS93 (18<=eta')

il Medico



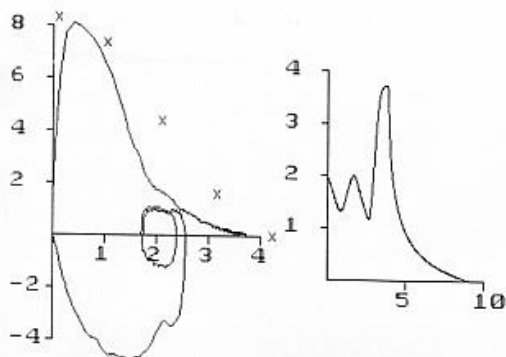
data: 09/12/2002

cartella n: 8303

|          |     | oss.  | teorici | %   | lim.      |
|----------|-----|-------|---------|-----|-----------|
| VC       | l   | 3.83  | 4.42    | 87  | 3.50-5.34 |
| IVC      | l   | 3.74  | 4.42    | 85  | 3.50-5.34 |
| FVC      | l   | 3.74  | 4.24    | 88  | 3.24-5.24 |
| FEV1     | l   | 2.70  | 3.31    | 82  | 2.47-4.15 |
| FEV1/VC  | %   | 70.50 | 75.75   | 93  | 64.0-87.6 |
| FEV1/FVC | %   | 72.19 |         |     |           |
| RV       | l   | 3.38  | 2.51    | 135 | 1.84-3.18 |
| FRC      | l   | 4.34  | 3.73    | 116 | 2.74-4.72 |
| TLC      | l   | 7.21  | 7.14    | 101 | 5.99-8.29 |
| RV/TLC   | %   | 46.85 | 38.53   | 122 | 29.5-47.5 |
| FRC/TLC  | %   | 60.24 | 57.26   | 105 | 46.2-68.4 |
| PEF      | l/s | 8.15  | 8.34    | 98  | 6.4-10.3  |
| MEF75    | l/s | 7.01  | 7.39    | 95  | 4.6-10.2  |
| MEF50    | l/s | 2.16  | 4.42    | 49  | 2.25-6.59 |
| MEF25    | l/s | 0.63  | 1.64    | 39  | 0.36-2.92 |
| FEF25-75 | l/s | 1.88  | 3.41    | 55  | 1.70-5.12 |

Teorici di Riferimento: Polgar 71 (6<eta'<18) ERS93 (18<=eta')

il Medico



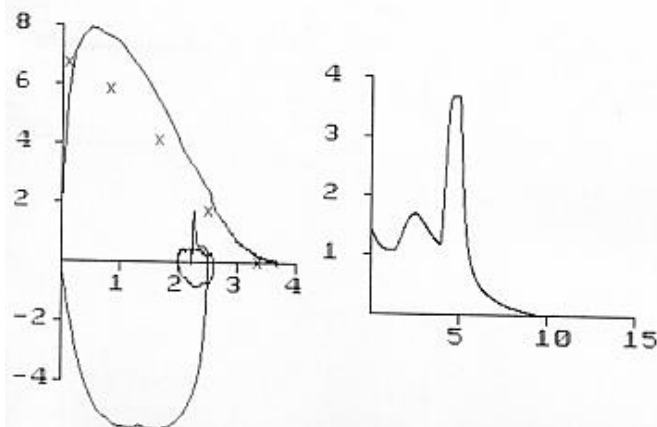
data: 25/11/2002

cartella n: 8253

|          |     | oss.  | teorici | %   | lim.      |
|----------|-----|-------|---------|-----|-----------|
| VC       | l   | 3.80  | 3.36    | 113 | 2.67-4.05 |
| IVC      | l   | 3.80  | 3.45    | 110 | 2.76-4.14 |
| FVC      | l   | 3.70  | 3.35    | 110 | 2.64-4.06 |
| FEV1     | l   | 3.12  | 2.89    | 108 | 2.27-3.51 |
| FEV1/VC  | %   | 82.05 | 80.27   | 102 | 69.6-91.0 |
| FEV1/FVC | %   | 84.26 |         |     |           |
| RV       | l   | 1.36  | 1.78    | 77  | 1.20-2.36 |
| FRC      | l   | 2.36  | 2.81    | 84  | 1.99-3.63 |
| TLC      | l   | 5.16  | 5.30    | 97  | 4.31-6.29 |
| RV/TLC   | %   | 26.39 | 34.37   | 77  | 24.8-44.0 |
| FRC/TLC  | %   | 45.66 | 52.45   | 87  | 42.7-62.3 |
| PEF      | l/s | 7.94  | 6.76    | 118 | 5.28-8.24 |
| MEF75    | l/s | 7.58  | 5.85    | 130 | 3.63-8.07 |
| MEF50    | l/s | 4.95  | 4.12    | 120 | 2.31-5.93 |
| MEF25    | l/s | 1.40  | 1.72    | 81  | 0.59-2.85 |
| FEF25-75 | l/s | 3.92  | 3.46    | 113 | 2.06-4.86 |

Teorici di Riferimento: Polgar 71 (6<eta'<18) ERS93 (18<=eta')

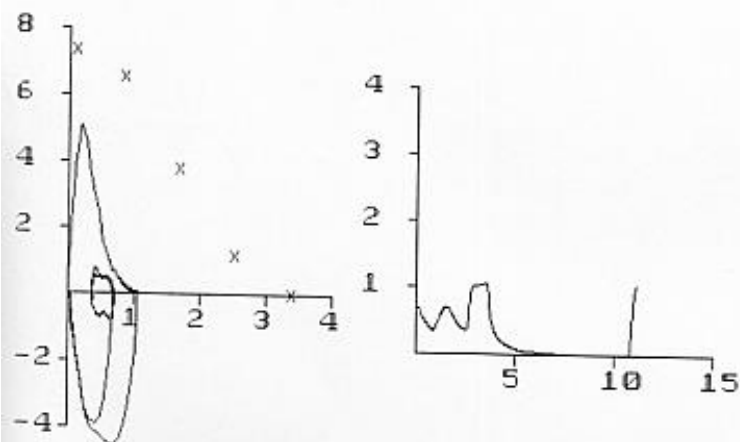
il Medico



|          |     | oss.  | teorici | %   | lim.       | post-br | %/oss. |
|----------|-----|-------|---------|-----|------------|---------|--------|
| VC       | l   | 1.06  | 3.51    | 30  | 2.59-4.43  | 1.00    | 94     |
| ERV      | l   | 0.29  |         |     |            |         |        |
| IVC      | l   | 1.06  | 3.51    | 30  | 2.59-4.43  |         |        |
| FVC      | l   | 1.06  | 3.39    | 31  | 2.39-4.39  | 1.00    | 94     |
| FEV1     | l   | 0.93  | 2.63    | 35  | 1.79-3.47  | 0.90    | 97     |
| FEV1/VC  | %   | 87.22 | 75.04   | 116 | 63.2-86.8  | 89.66   | 103    |
| FEV1/FVC | %   | 87.22 |         |     |            | 89.66   | 103    |
| RV       | l   | 0.88  | 2.43    | 36  | 1.76-3.10  |         |        |
| FRC      | l   | 1.20  | 3.45    | 35  | 2.46-4.44  |         |        |
| TLC      | l   | 1.94  | 6.11    | 32  | 4.96-7.26  |         |        |
| RV/TLC   | %   | 45.38 | 40.08   | 113 | 31.1-49.1  |         |        |
| FRC/TLC  | %   | 61.77 | 58.10   | 106 | 47.0-69.2  |         |        |
| PEF      | l/s | 5.12  | 7.37    | 69  | 5.38-9.36  | 4.64    | 91     |
| MEF75    | l/s | 4.61  | 6.57    | 70  | 3.76-9.38  | 3.79    | 82     |
| MEF50    | l/s | 1.75  | 3.80    | 46  | 1.63-5.97  | 1.25    | 72     |
| MEF25    | l/s | 0.45  | 1.19    | 38  | -0.09-2.47 | 0.37    | 82     |
| FEF25-75 | l/s | 1.27  | 2.98    | 43  | 1.27-4.69  | 1.10    | 87     |

Teorici di Riferimento: Polgar 71 (6<eta'<18) ERS93 (18<=eta')

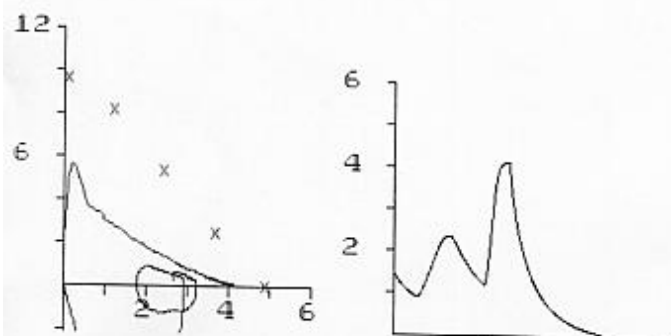
il Medico



|           |     | oss.  | teorici | %   | lim.      | post-br | %/oss. |
|-----------|-----|-------|---------|-----|-----------|---------|--------|
| VC        | l   | 4.58  | 5.14    | 89  | 4.22-6.06 | 5.03    | 110    |
| IVC       | l   | 4.48  | 5.14    | 87  | 4.22-6.06 |         |        |
| FVC       | l   | 4.14  | 4.91    | 84  | 3.91-5.91 | 5.03    | 122    |
| FEV1      | l   | 2.54  | 4.18    | 61  | 3.34-5.02 | 3.66    | 144    |
| FEV1/VC   | %   | 55.42 | 82.74   | 67  | 70.9-94.5 | 72.83   | 131    |
| FEV1/FVC  | %   | 61.35 |         |     |           | 72.83   | 119    |
| RV        | l   | 2.50  | 1.57    | 159 | 0.90-2.24 |         |        |
| FRC       | l   | 3.22  | 3.17    | 102 | 2.18-4.16 |         |        |
| TLC       | l   | 7.09  | 6.67    | 106 | 5.52-7.82 |         |        |
| RV/TLC    | %   | 35.33 | 23.43   | 151 | 14.4-32.4 |         |        |
| FRC/TLC   | %   | 45.43 | 49.07   | 93  | 38.0-60.2 |         |        |
| PEF       | l/s | 5.68  | 9.65    | 59  | 7.7-11.6  | 7.38    | 130    |
| MEF75     | l/s | 3.05  | 8.19    | 37  | 5.4-11.0  | 6.48    | 212    |
| MEF50     | l/s | 1.76  | 5.40    | 33  | 3.23-7.57 | 4.01    | 228    |
| MEF25     | l/s | 0.77  | 2.49    | 31  | 1.21-3.77 | 2.21    | 288    |
| FIVC      | l   |       |         |     |           | 4.03    |        |
| FIV1      | l   |       |         |     |           | 4.03    |        |
| PIF       | l/s |       |         |     |           | 6.96    |        |
| FEV1/FIV1 | %   |       |         |     |           | 90.97   |        |
| FEF25-75  | l/s | 1.57  | 4.97    | 32  | 3.26-6.68 | 3.84    | 245    |

Teorici di Riferimento: Polgar 71 (6<eta'<18) ERS93 (18<=eta')

il Medico



cod.: Amb. centro asma

peso: 83.0 c.r.:

ind.:

tel.:

data: 18/01/2002

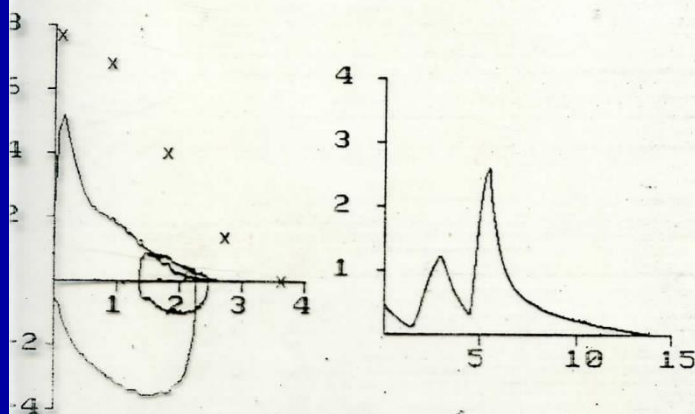
cartella n: 7135

VALORI SPIROMETRICI A RIPOSO E POST BRONCODILATATORE

|           |     | oss.  | teorici | %  | lim.      | post-br | %/oss. |
|-----------|-----|-------|---------|----|-----------|---------|--------|
| VC        | l   | 2.76  | 3.77    | 73 | 2.85-4.69 | 3.05    | 110    |
| IVC       | l   | 2.76  | 3.77    | 73 | 2.85-4.69 |         |        |
| FVC       | l   | 2.60  | 3.63    | 72 | 2.63-4.63 | 3.05    | 117    |
| FEV1      | l   | 1.72  | 2.86    | 60 | 2.02-3.70 | 2.11    | 123    |
| FEV1/VC   | %   | 62.27 | 75.93   | 82 | 64.1-87.7 | 69.27   | 111    |
| PEF       | l/s | 5.23  | 7.71    | 68 | 5.72-9.70 | 6.63    | 127    |
| MEF75     | l/s | 2.33  | 6.82    | 34 | 4.01-9.63 | 3.87    | 166    |
| MEF50     | l/s | 1.34  | 4.03    | 33 | 1.86-6.20 | 2.19    | 163    |
| MEF25     | l/s | 0.32  | 1.38    | 23 | 0.10-2.66 | 0.99    | 309    |
| FIVC      | l   |       |         |    |           | 2.74    |        |
| FIV1      | l   |       |         |    |           | 2.74    |        |
| PIF       | l/s |       |         |    |           | 4.47    |        |
| FEV1/FIV1 | %   |       |         |    |           | 77.03   |        |

Teorici di riferimento: POLGAR 71 ( 6<eta'<18 ) CECA 83 ( 18<=eta'<80 )

il Medico

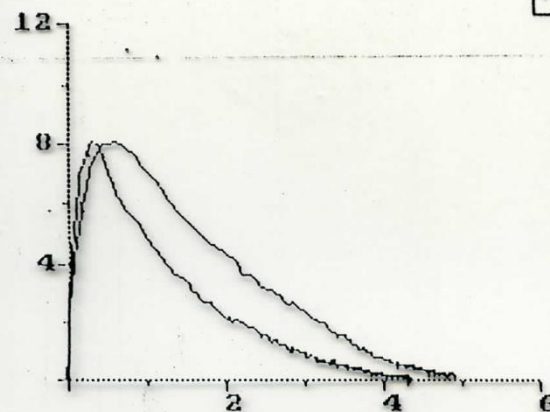


25gen1999 14:37 20°C 777mmHg

MIGLIORE CURVA BASALE E POSTBRONCODILATATORE

n. 2572

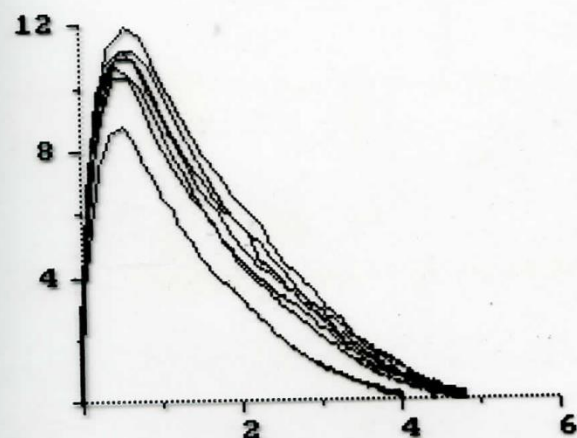
M 27anni 176cm 95Kg



Criterio applicato: A7894  
Test in esecuzione  
prove accettabili 2/2  
riprod FVC 180 ml (3.7%)  
riprod FEV1 180 ml (5.0%)

|     | FVC  | FEV1 | PEF  | DtPEF | Vext | FET | Plat | C |
|-----|------|------|------|-------|------|-----|------|---|
| obr | 4.92 | 3.61 | 8.04 | 79    | 2.0% | 4.9 | 0.2  | B |
| bas | 4.34 | 2.81 | 8.05 | 49    | 1.4% | 7.5 | 0.6  | B |





Test di provocazione bronchiale con metacolina

06lug2000 11:55 27°C 771mmHg

M 39anni 178cm 91Kg

|      | Dose  | FEV1 | %   | FVC  | %   |
|------|-------|------|-----|------|-----|
| 6-30 | 4.000 | 3.80 | -5  | 4.69 | -3  |
| 6-90 | 4.000 | 3.81 | -5  | 4.75 | -2  |
| 6-5' | 4.000 | 3.57 | -11 | 4.41 | -9  |
| 7-30 | 8.000 | 3.11 | -23 | 4.01 | -17 |

PC- 10 FEV1  
4.0000

PC- 20 FEV1  
6.8380

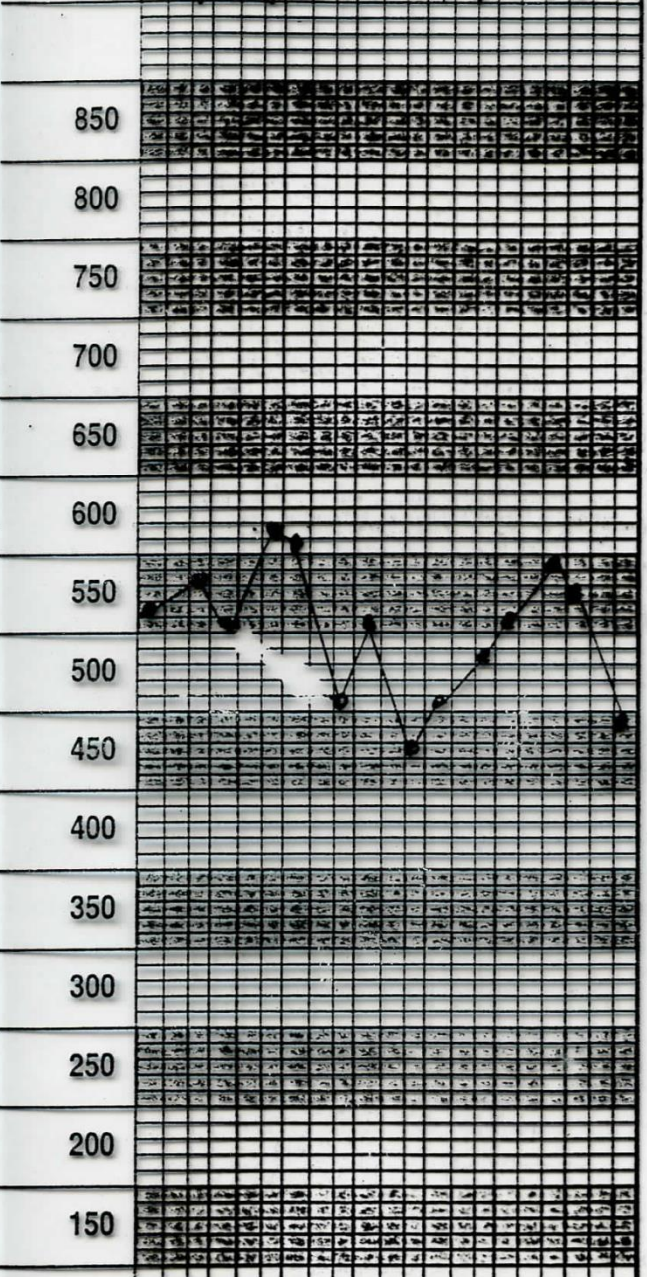
PC- 10 FVC  
4.4684

PC- 20 FVC



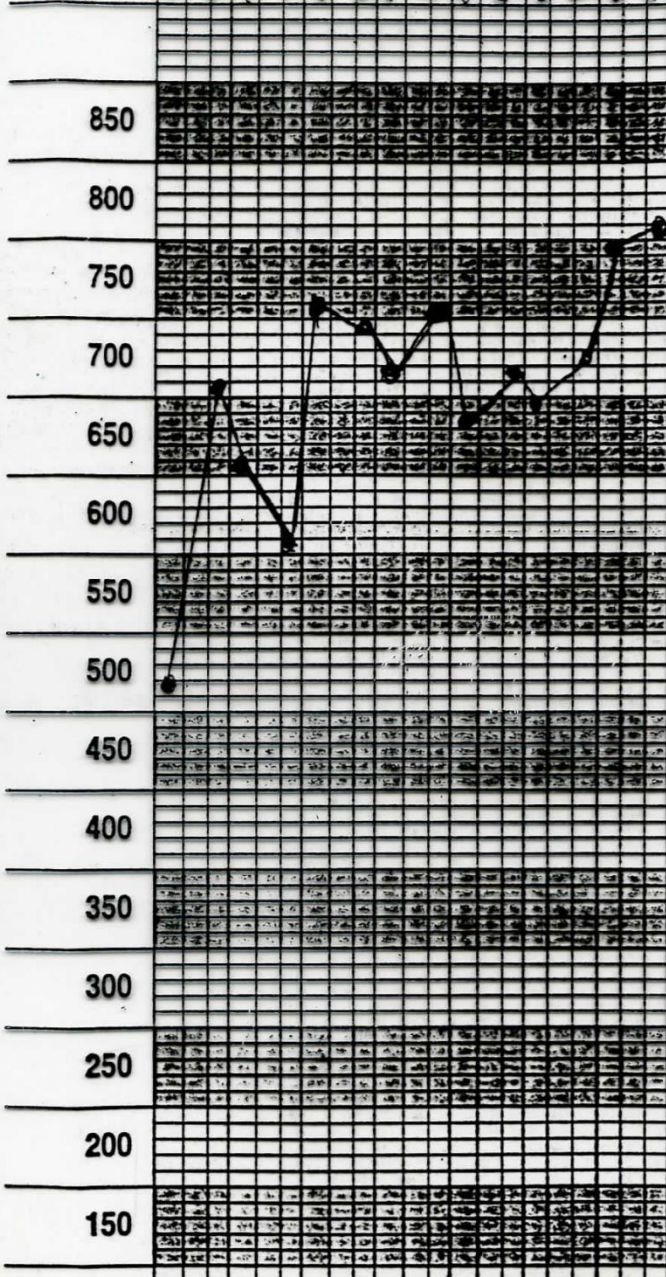
Nome NICOTRA

| Data | 6 | 7  | 8  | 9 | 10 | 11 | 12 |
|------|---|----|----|---|----|----|----|
| Ora  | 8 | 15 | 31 | 5 | 21 | 5  | 21 |



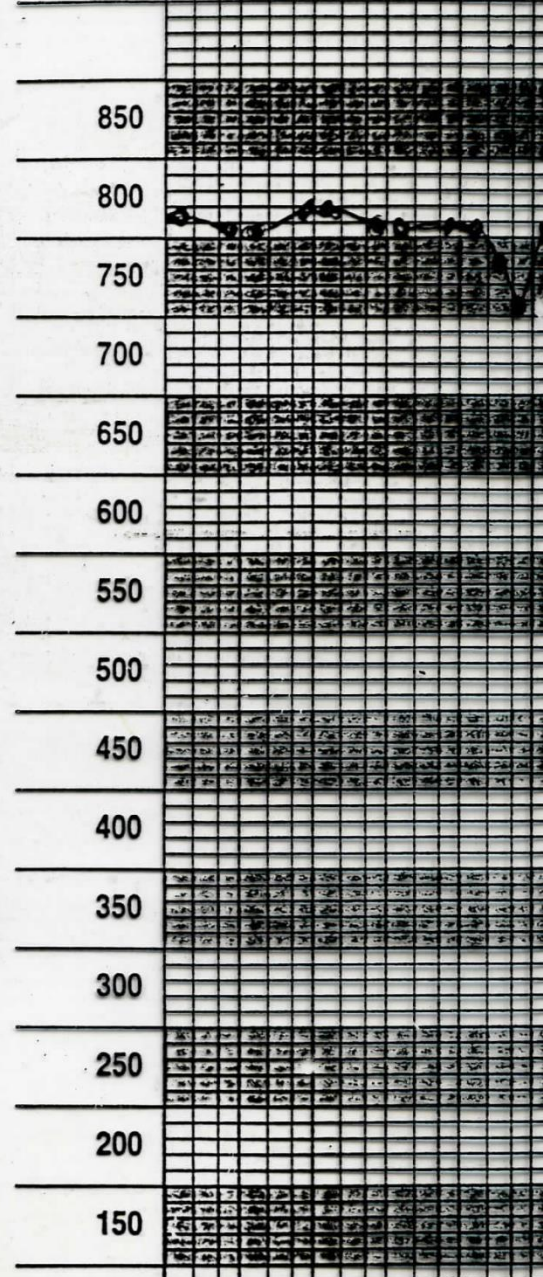
Nome

| Data | 13 | 14 | 15 | 16 | 17 | 18 | 19 |
|------|----|----|----|----|----|----|----|
| Ora  | 6  | 9  | 6  | 0  | 6  | 21 | 6  |



Nome ALIRU

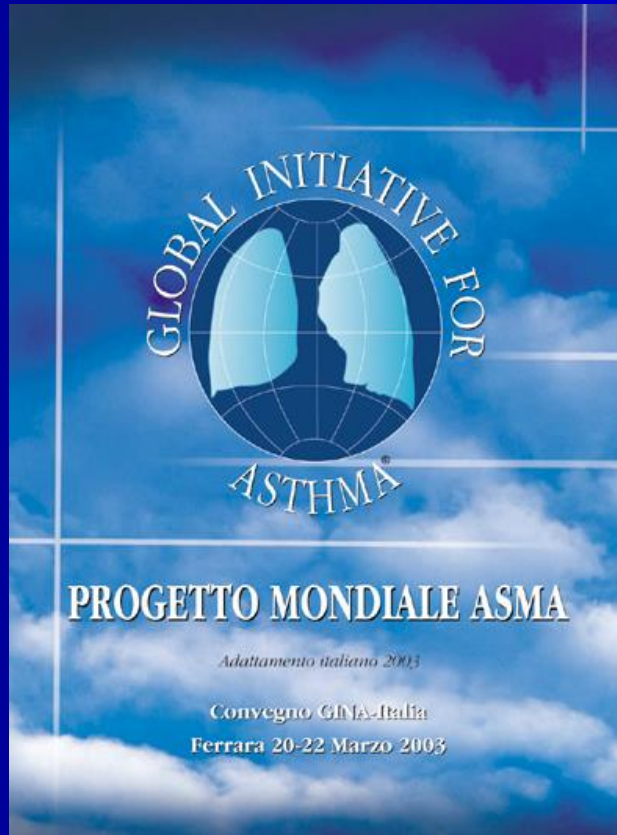
| Data | 20 | 21 | 22 | 23 | 24 |
|------|----|----|----|----|----|
| Ora  | 5  | 21 | 5  | 21 | 5  |





# Rapporto del Gruppo di Lavoro del GINA

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## Argomenti:

- **Definizione**
- Epidemiologia ed impatto socio-economico dell'asma
- Fattori di rischio
- Patogenesi
- Diagnosi e Classificazione
- Educazione del paziente e somministrazione delle cure
- Programma di trattamento dell'asma in sei parti
- Raccomandazioni per la ricerca

# Definition of asthma

Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation.

It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation.

# Asma bronchiale: definizione

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L'asma è una malattia infiammatoria cronica delle vie aeree caratterizzata da:

- Episodi ricorrenti di dispnea, respiro sibilante, tosse e senso di costrizione toracica
- Ostruzione bronchiale (di solito reversibile spontaneamente o dopo trattamento farmacologico)
- Iperreattività bronchiale
- Infiltrazione di cellule infiammatorie, rilascio di mediatori e rimodellamento strutturale delle vie aeree

# Rapporto del Gruppo di Lavoro del GINA

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## Argomenti:

- Definizione
- **Epidemiologia ed impatto socio-economico dell'asma**
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- Raccomandazioni per la ricerca

# Epidemiologia dell'asma

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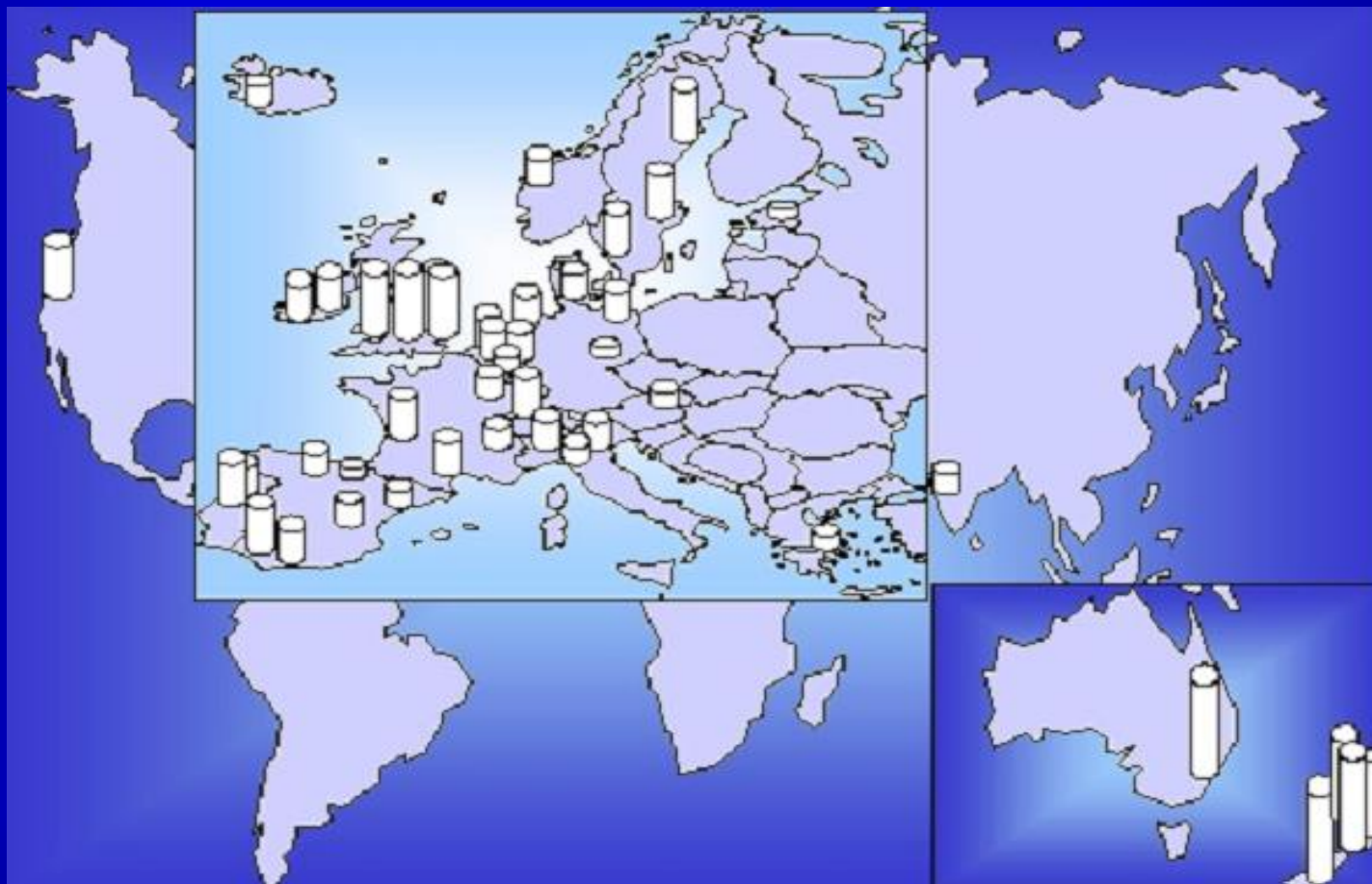
- L'asma è una delle patologie più diffuse al mondo
- L'asma è diffusa in tutti i paesi ma varia in modo considerevole da nazione a nazione e può mostrare variazioni anche all'interno della stessa nazione
- La variazione geografica è confermata anche dalla distribuzione dell'atopia e della reattività bronchiale
- La variazione geografica è simile per bambini e adulti
- In Italia la prevalenza di asma è più bassa rispetto a quella di molte altre nazioni, soprattutto dei paesi anglosassoni, sia nella popolazione infantile sia negli adulti

# Burden of asthma

- Asthma is one of the most common chronic diseases worldwide with an estimated 300 million affected individuals
- Prevalence is increasing in many countries, especially in children
- Asthma is a major cause of school and work absence
- Health care expenditure on asthma is very high
  - Developed economies might expect to spend 1-2 percent of total health care expenditures on asthma.
  - Developing economies likely to face increased demand due to increasing prevalence of asthma
  - Poorly controlled asthma is expensive
  - However, investment in prevention medication is likely to yield cost savings in emergency care

## Distribuzione geografica della prevalenza dell' asma in atto – ECRHS

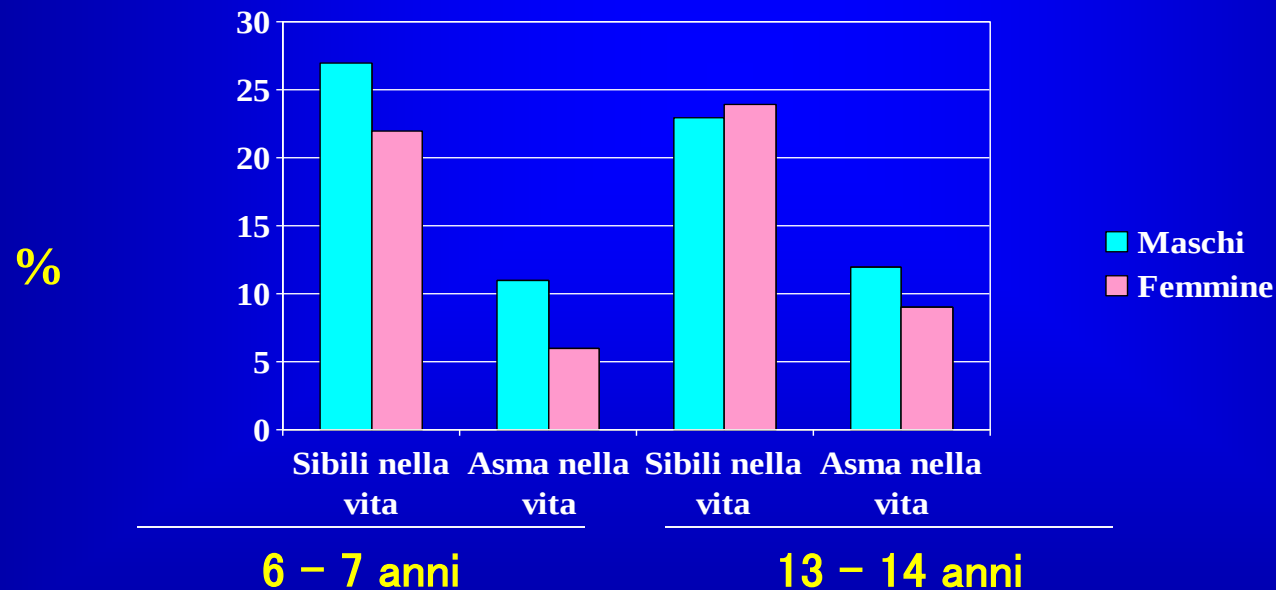
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# Prevalenza di sibili e asma in bambini ed adolescenti italiani

Studio SIDRIA (1994–95)



SIDRIA Collaborative Group – Eur Respir J 1997; Eur Respir J 1999

# Epidemiologia dell'asma

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Negli ultimi 20 anni la prevalenza di asma è aumentata considerevolmente in molti paesi, soprattutto nei bambini

# Epidemiologia dell'asma

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- Alcune evidenze, anche italiane, sembrerebbero documentare che la prevalenza di asma e delle manifestazioni asmatiche non e' attualmente in ulteriore aumento
- La stabilizzazione della prevalenza della sintomatologia asmatica, secondo alcuni studi, anche italiani, essere associata sembra all'incremento dei trattamenti antiasmatici

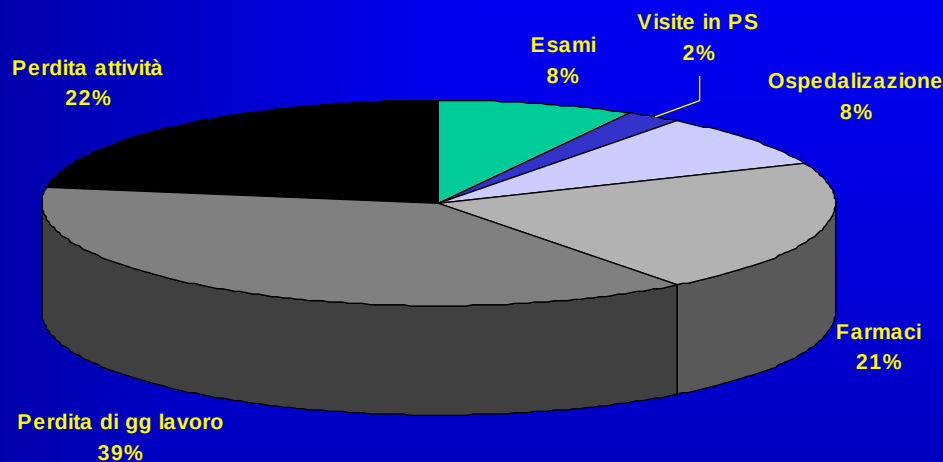
# Epidemiologia dell'asma

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L'attuale prevalenza di asma in Italia, benché inferiore a quella di molte altre nazioni, rappresenta una notevole fonte di costi sia sociali sia umani

# Componenti del costo medio annuale di un paziente adulto asmatico in Italia (studio ISAYA)

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# Rapporto del Gruppo di Lavoro del GINA

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## Argomenti:

- Definizione
- Epidemiologia ed impatto socio-economico dell'asma
- **Fattori di rischio**
- **Patogenesi (anatomia patologica)**
- Diagnosi e Classificazione
- Educazione del paziente e somministrazione delle cure
- Programma di trattamento dell'asma in sei parti
- Raccomandazioni per la ricerca

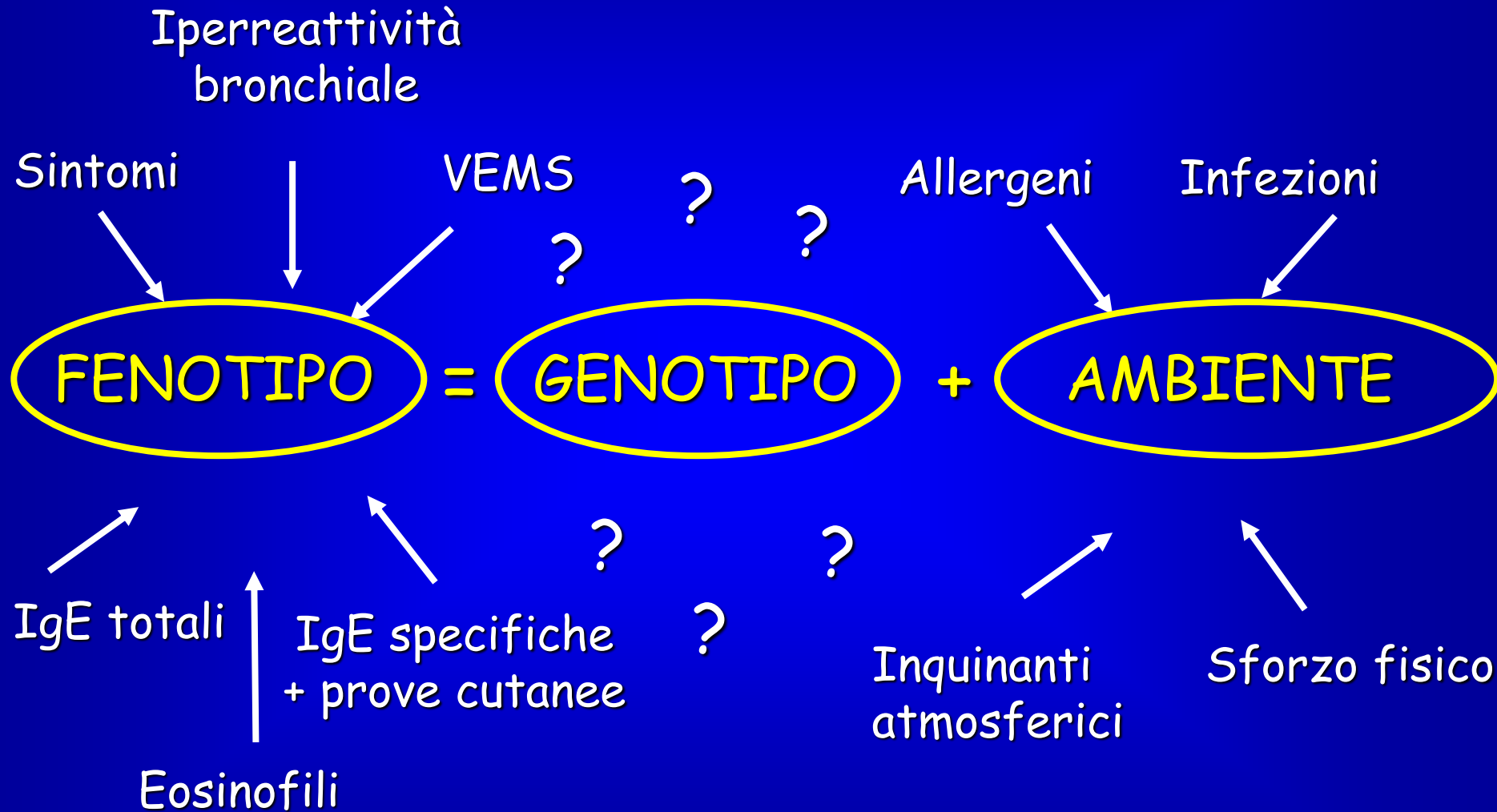


# Fattori di rischio di asma

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- Fattori individuali: predispongono l'individuo all'asma
- Fattori ambientali:
  - influenzano la possibilità di sviluppare asma in soggetti predisposti,
  - scatenano le riacutizzazioni e/o causano la persistenza dei sintomi

# ASMA = MALATTIA GENETICA COMPLESSA



# Fattori di rischio di asma

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## Fattori individuali

- Predisposizione genetica
- Atopia
- Iperresponsività delle vie aeree
- Sesso
- Razza/etnia

## Fattori ambientali

- Allergeni
- Sensibilizzanti professionali
- Fumo di tabacco
- Inquinamento atmosferico
- Infezioni delle vie respiratorie
- Fattori socio-economici
- Dimensioni del nucleo familiare
- Additivi alimentari e farmaci
- Obesità
- Infezioni parassitarie

# Fattori in grado di indurre riacutizzazioni asmatiche

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- Infezioni delle vie respiratorie
- Allergeni
- Inquinanti atmosferici interni (fumo, ecc..) ed esterni (urbani, industriali, ecc..)
- Esercizio fisico
- Fattori meteorologici
- Farmaci
- Alimenti

# Riacutizzazioni asmatiche e virus respiratori

---

- Le infezioni virali sono causa frequente di riacutizzazioni asmatiche
- I soggetti asmatici sono più suscettibili all'infezione da rinovirus
- E' dimostrato un sinergismo tra infezioni virali ed esposizione ad allergeni nell'indurre le riacutizzazioni e nel determinare la gravità delle riacutizzazioni



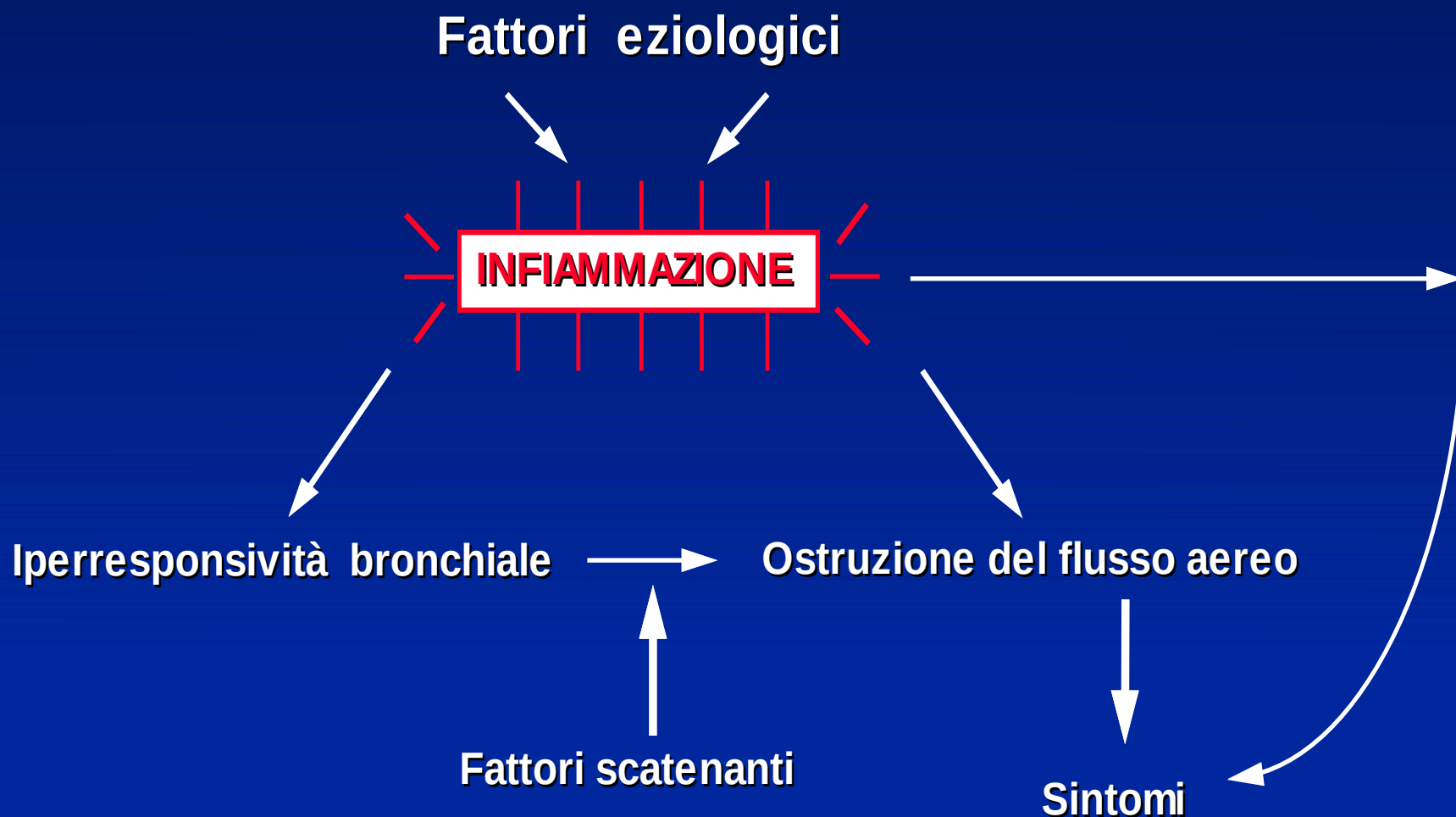
# Progetto Mondiale Asma

- ◆ Epidemiologia
- ◆ Definizione
- ➡ ◆ **CAUSE E MECCANISMI**
- ◆ Diagnosi
- ◆ Classificazione
- ◆ Trattamento
- ◆ Istruzione del paziente
- ◆ Prevenzione
- ◆ Aspetti socio-economici
- ◆ Organizzazione sanitaria



# Progetto Mondiale Asma

## PATOGENESI





## Eosinophilic asthma

### Allergic eosinophilic inflammation

- Eosinophil ++
- Neutrophil -
- Epithelial damage ++
- Mucus +
- Reticular basement membrane thickening ++
- Airway smooth muscle mass ++

### Non-allergic eosinophilic inflammation

- Eosinophil ++
- Neutrophil -
- Epithelial damage ++
- Mucus +
- Reticular basement membrane thickening ++
- Airway smooth muscle mass ++

## Health

Airway smooth muscle

Epithelium and reticular basement membrane

Allergens

Pollutants, oxidative stress

Pollutants, microbes

Pollutants, oxidative stress, microbes

## Non-eosinophilic asthma

### Paucigranulocytic

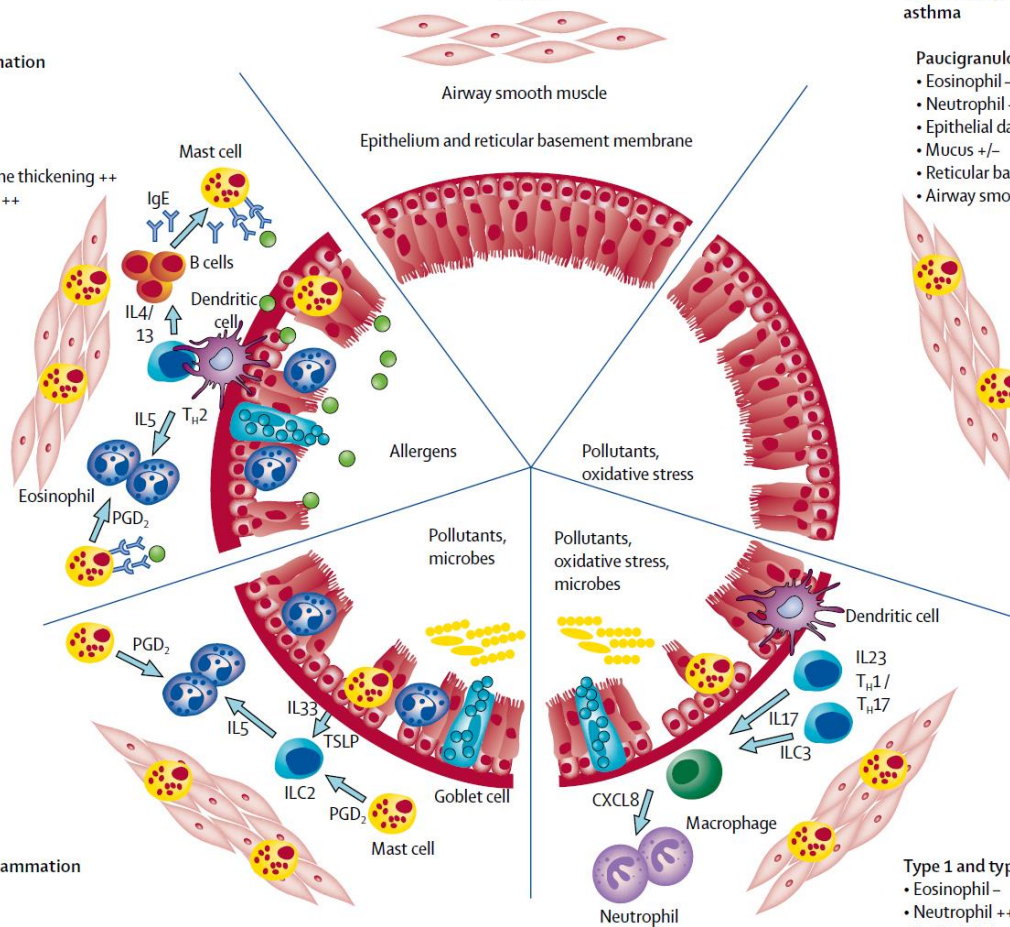
- Eosinophil -
- Neutrophil -
- Epithelial damage +
- Mucus +/-
- Reticular basement membrane thickening +/-
- Airway smooth muscle mass +

### Type 1 and type 17 neutrophilic inflammation

- Eosinophil -
- Neutrophil ++
- Epithelial damage ++
- Mucus ++
- Reticular basement membrane thickening +
- Airway smooth muscle mass +

### Mixed granulocytic asthma

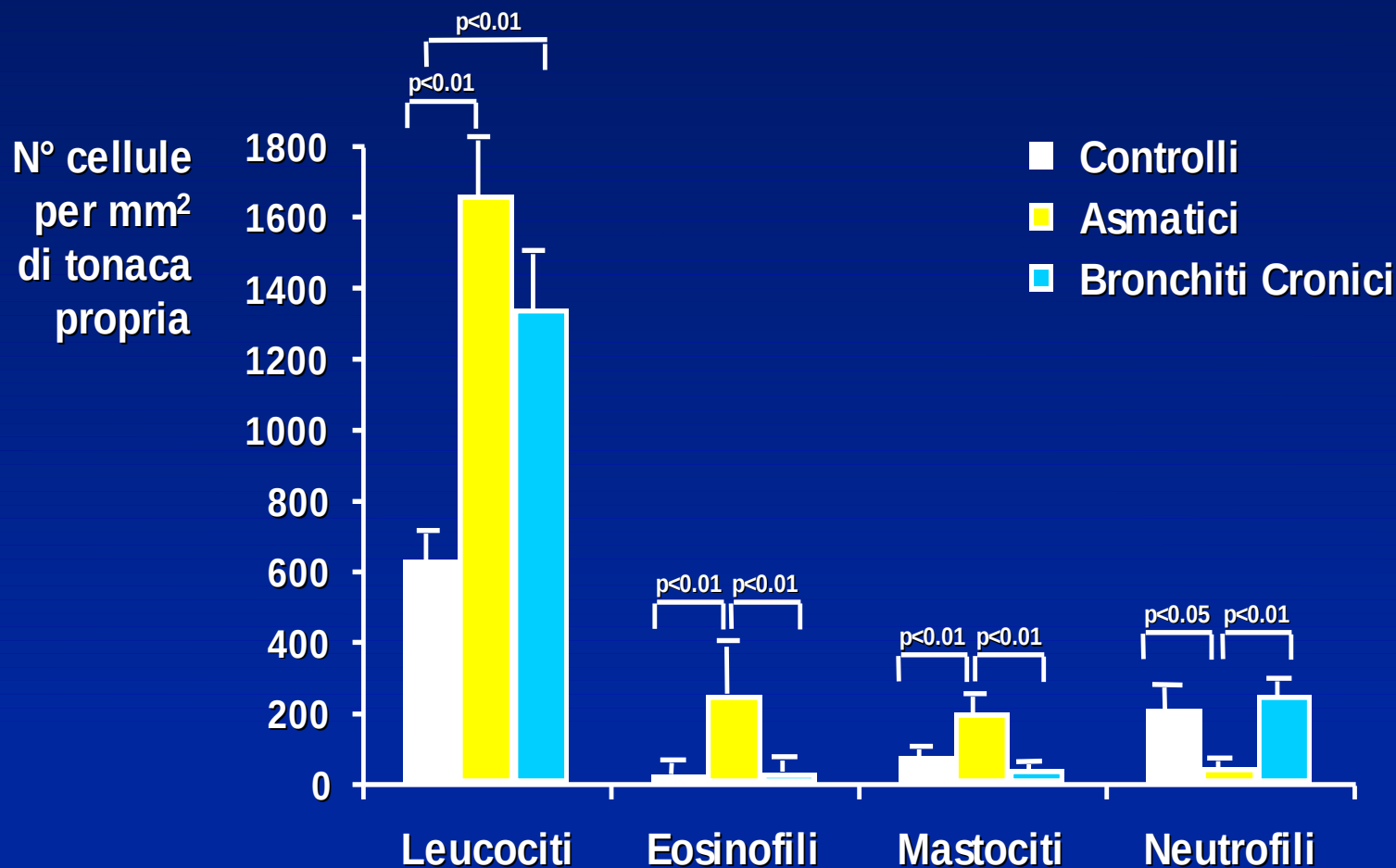
- Eosinophil +
- Neutrophil +
- Epithelial damage ++
- Mucus ++
- Reticular basement membrane thickening +
- Airway smooth muscle +





## Progetto Mondiale Asma

# QUADRO ANATOMO - PATOLOGICO

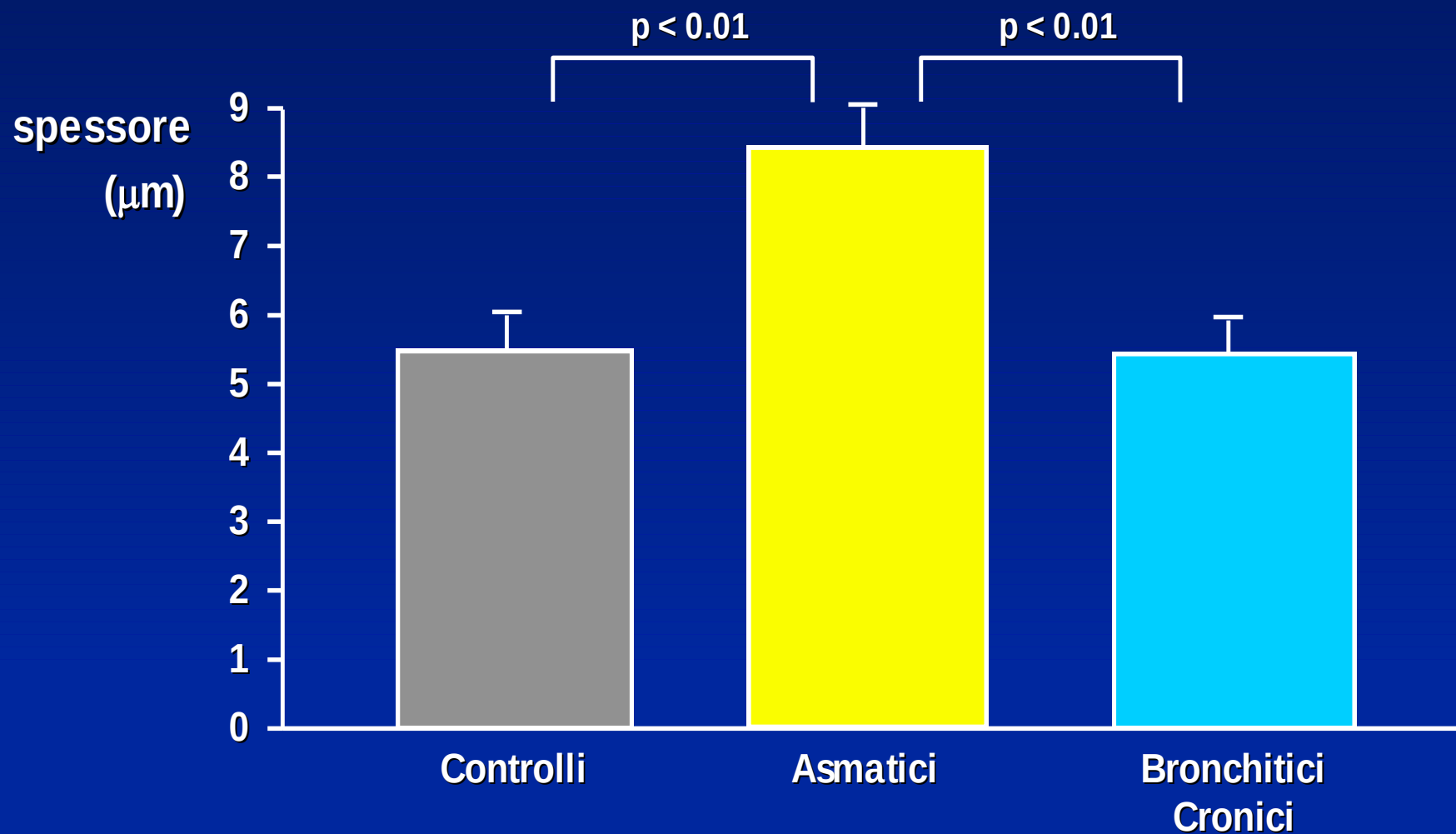




## Progetto Mondiale Asma

# QUADRO ANATOMO - PATOLOGICO

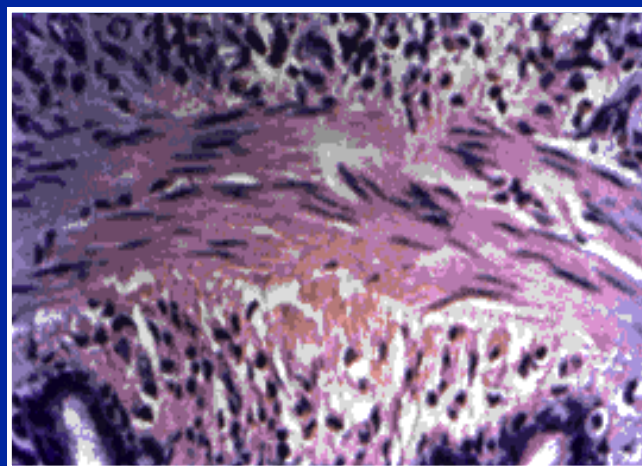
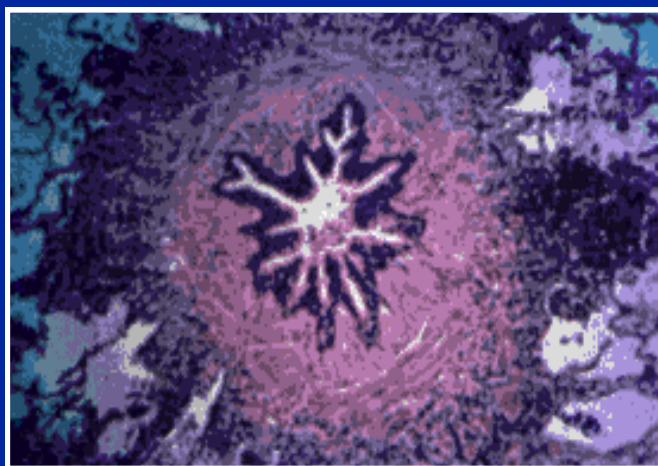
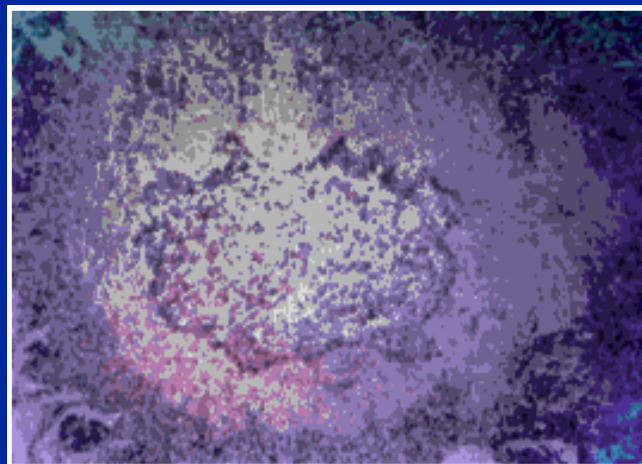
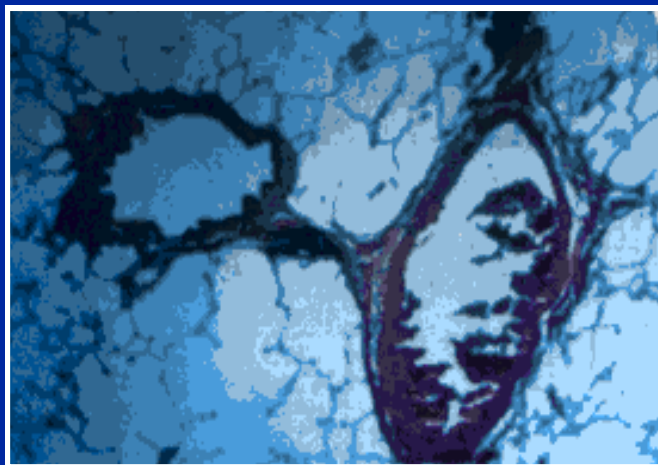
## Membrana basale dell'epitelio bronchiale





# Progetto Mondiale Asma

## **MORTE PER ASMA**



# Rapporto del Gruppo di Lavoro del GINA

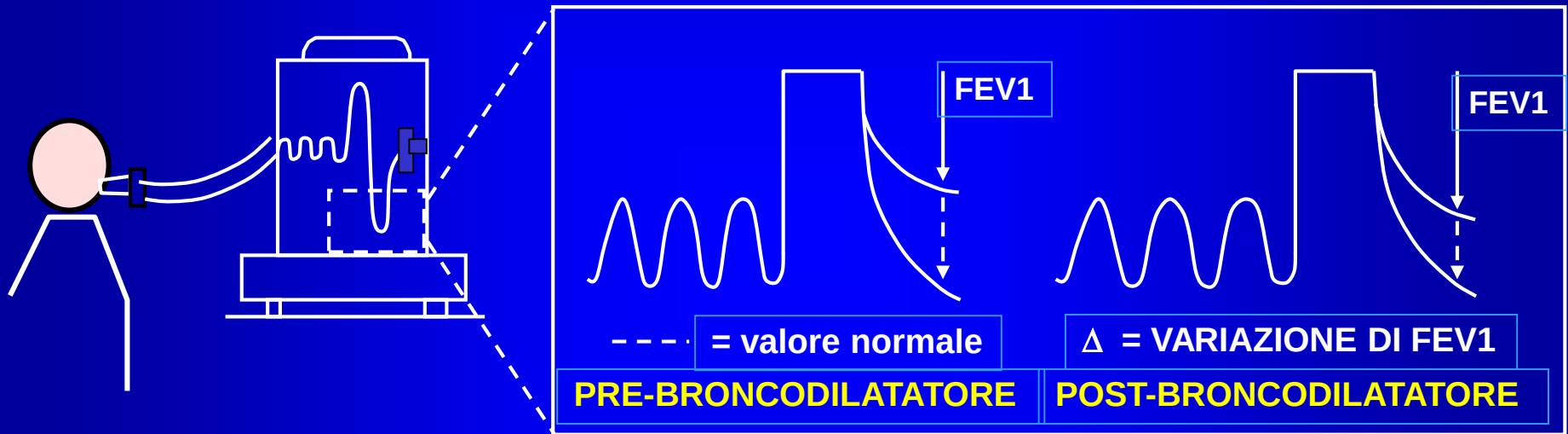
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## Argomenti:

- Definizione
- Epidemiologia ed impatto socio-economico dell'asma
- Fattori di rischio
- Patogenesi
- **Diagnosi e Classificazione**
- Educazione del paziente e somministrazione delle cure
- Programma di trattamento dell'asma in sei parti
- Raccomandazioni per la ricerca

# BRONCOPNEUMOPATIA CRONICA OSTRUTTIVA



**OSTRUZIONE BRONCHIALE  
reversibile**





Progetto Mondiale Asma

## **DIAGNOSI CLINICA DI ASMA**

- Anamnesi ed esame clinico
- Prove funzionali respiratorie  $\pm$  broncodilatatore

### **CASI DUBBI:**

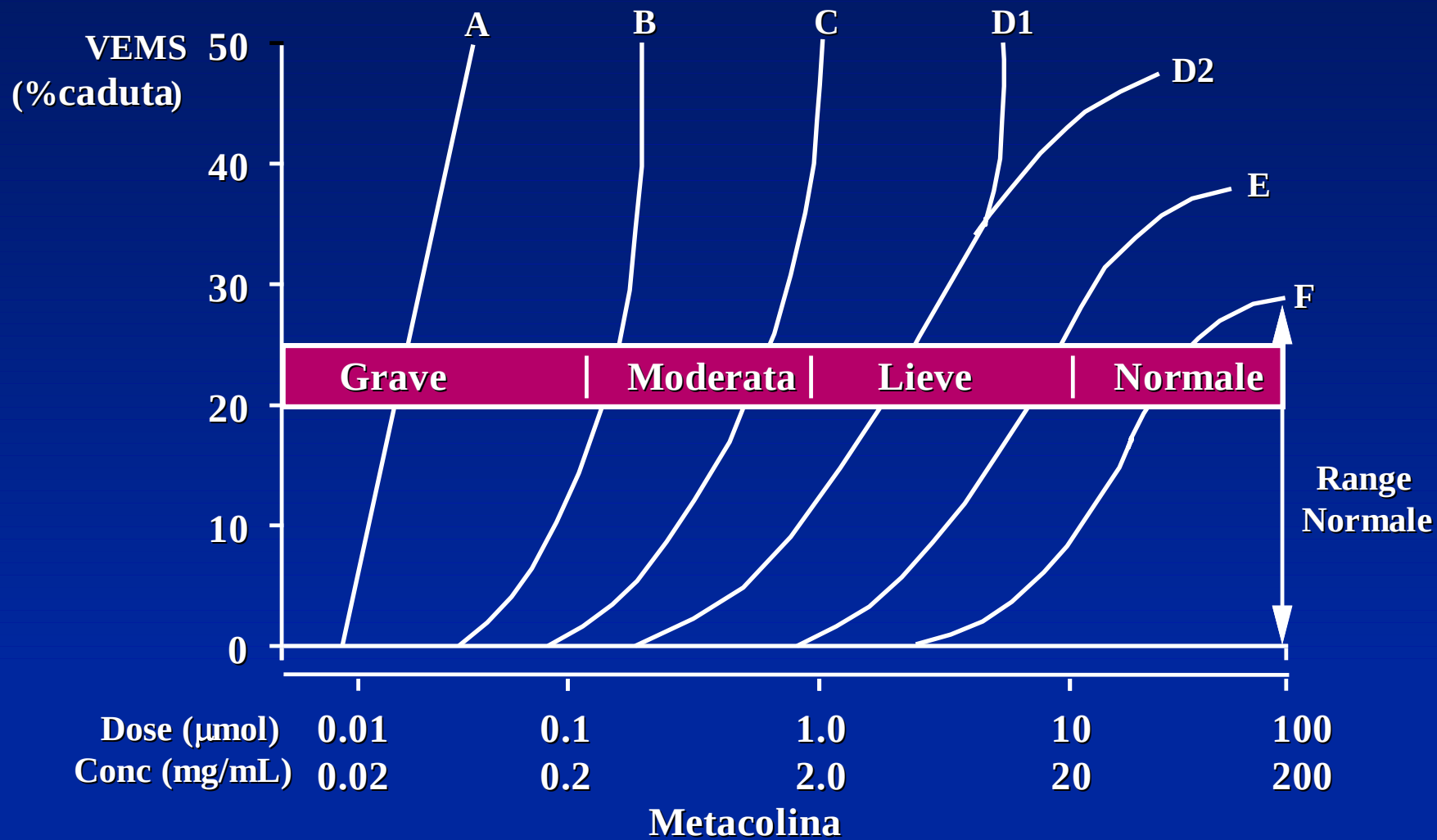
- Test con metacolina
- Risposta alla terapia antiasmatica

### **DIAGNOSI EZIOLOGICA**



# Progetto Mondiale Asma

## TEST ALLA METACOLINA





# Classificazione di Gravità

## CLASSIFICAZIONE DI GRAVITA' Caratteristiche cliniche in assenza di terapia

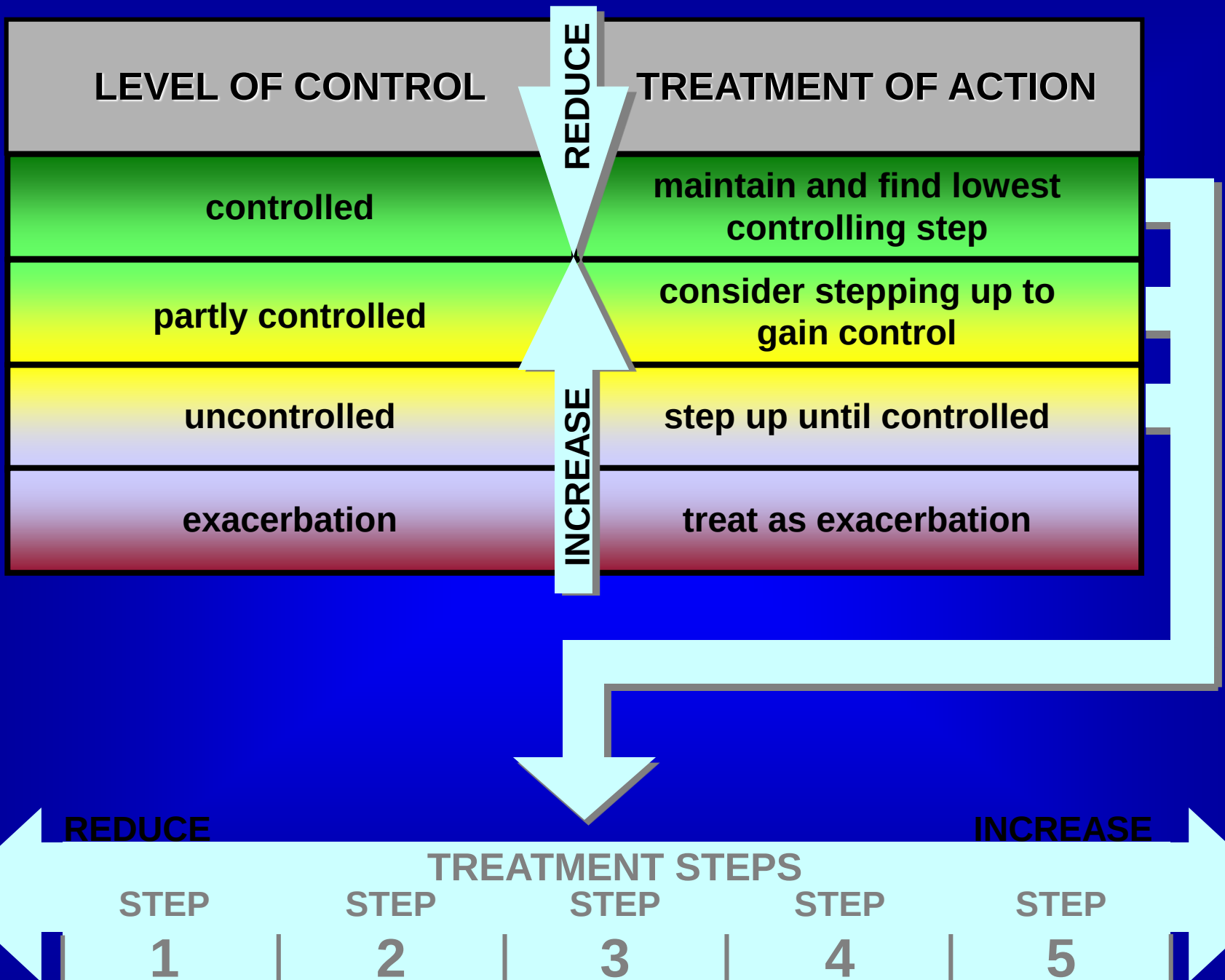
|                                                        | Sintomi                                                                      | Sintomi notturni            | FEV <sub>1</sub> o PEF                 |
|--------------------------------------------------------|------------------------------------------------------------------------------|-----------------------------|----------------------------------------|
| <b>STEP 4</b><br><b>Grave</b><br><b>Persistente</b>    | Continui<br>Attività fisica limitata                                         | Frequenti                   | ≤ 60% predetto<br>Variabilità > 30%    |
| <b>STEP 3</b><br><b>Moderato</b><br><b>Persistente</b> | Quotidiani<br>Attacchi che limitano<br>L'attività                            | ➤ 1 volta<br>Alla settimana | 60 - 80% predetto<br>Variabilità > 30% |
| <b>STEP 2</b><br><b>Lieve</b><br><b>Persistente</b>    | > 1 volta/settimana<br>ma < 1 volta / giorno                                 | > 2 volte al mese           | ≥ 80% predetto<br>Variabilità 20 - 30% |
| <b>STEP 1</b><br><b>Intermittente</b>                  | < 1 volta/settimana<br>Asintomatico e con<br>normale PEF tra gli<br>attacchi | ≤ 2 volte al mese           | ≥ 80% predetto<br>Variabilità < 20%    |

La presenza di almeno uno dei criteri di gravità è sufficiente per classificare un paziente in un determinato livello di gravità



# Levels of Asthma Control

| <i>Characteristic</i>                         | <b>Controlled</b><br>(All of the following) | <b>Partly controlled</b><br>(Any present in any week)            | <b>Uncontrolled</b>                                                       |
|-----------------------------------------------|---------------------------------------------|------------------------------------------------------------------|---------------------------------------------------------------------------|
| <b>Daytime symptoms</b>                       | <b>None (2 or less / week)</b>              | <b>More than twice / week</b>                                    | <b>3 or more features of partly controlled asthma present in any week</b> |
| <b>Limitations of activities</b>              | <b>None</b>                                 | <b>Any</b>                                                       |                                                                           |
| <b>Nocturnal symptoms / awakening</b>         | <b>None</b>                                 | <b>Any</b>                                                       |                                                                           |
| <b>Need for rescue / “reliever” treatment</b> | <b>None (2 or less / week)</b>              | <b>More than twice / week</b>                                    |                                                                           |
| <b>Lung function (PEF or FEV<sub>1</sub>)</b> | <b>Normal</b>                               | <b>&lt; 80% predicted or personal best (if known) on any day</b> |                                                                           |
| <b>Exacerbation</b>                           | <b>None</b>                                 | <b>One or more / year</b>                                        | <b>1 in any week</b>                                                      |



**REDUCE**

**INCREASE**

## TREATMENT STEPS

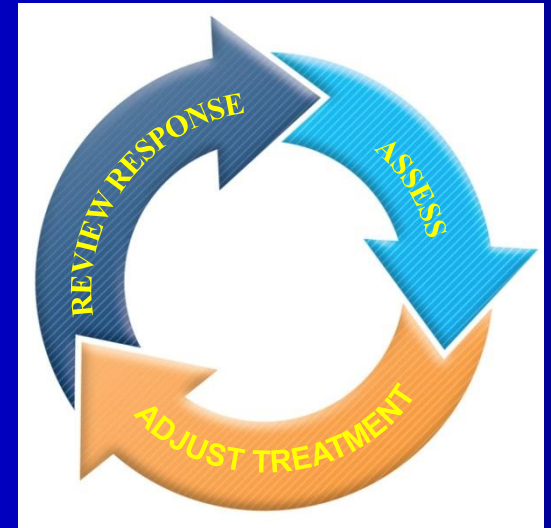
| STEP<br>1                                 | STEP<br>2                                 | STEP<br>3                                               | STEP<br>4                                                                  | STEP<br>5                              |
|-------------------------------------------|-------------------------------------------|---------------------------------------------------------|----------------------------------------------------------------------------|----------------------------------------|
| asthma education                          |                                           |                                                         |                                                                            |                                        |
| environmental control                     |                                           |                                                         |                                                                            |                                        |
| as needed rapid-acting $\beta_2$ -agonist | as needed rapid-acting $\beta_2$ -agonist |                                                         |                                                                            |                                        |
| CONTROLLER OPTIONS                        | SELECT ONE                                | SELECT ONE                                              | ADD ONE OR MORE                                                            | ADD ONE OR BOTH                        |
|                                           | low-dose ICS*                             | low-dose ICS <i>plus</i> long-acting $\beta_2$ -agonist | medium- <i>or</i> high-dose ICS <i>plus</i> long-acting $\beta_2$ -agonist | oral glucocorticosteroid (lowest dose) |
|                                           | leukotriene modifier**                    | medium- <i>or</i> high-dose ICS                         | leukotriene modifier                                                       | anti-IgE treatment                     |
|                                           |                                           | low-dose ICS <i>plus</i> leukotriene modifier           | sustained-release theophylline                                             |                                        |
|                                           |                                           | low-dose ICS <i>plus</i> sustained-release theophylline |                                                                            |                                        |
|                                           |                                           |                                                         |                                                                            |                                        |

\*inhaled glucocorticosteroids

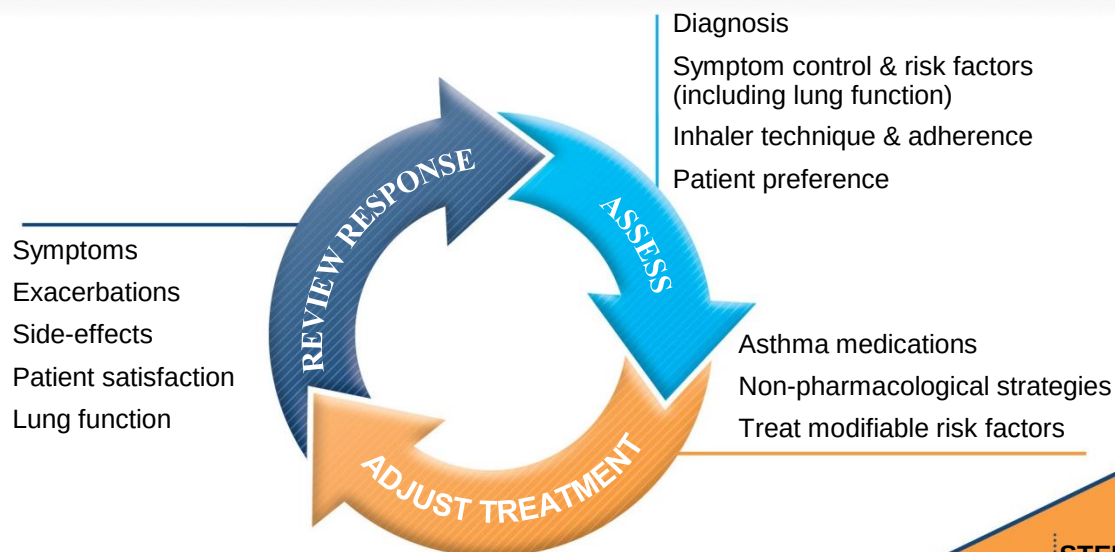
\*\* receptor antagonist or synthesis inhibitors

# Treating to control symptoms and minimize risk

- Establish a patient-doctor partnership
- Manage asthma in a continuous cycle:
  - **Assess**
  - **Adjust** treatment (pharmacological and non-pharmacological)
  - **Review** the response
- Teach and reinforce essential skills
  - Inhaler skills
  - Adherence
  - Guided self-management education
    - Written asthma action plan
    - Self-monitoring
    - Regular medical review



# Stepwise management - pharmacotherapy



**PREFERRED  
CONTROLLER  
CHOICE**

|                          | STEP 1                                      | STEP 2                                                            | STEP 3                                                    | STEP 4                                                       | STEP 5                                                           |
|--------------------------|---------------------------------------------|-------------------------------------------------------------------|-----------------------------------------------------------|--------------------------------------------------------------|------------------------------------------------------------------|
|                          |                                             | Low dose ICS                                                      | Low dose ICS/LABA**                                       | Med/high ICS/LABA                                            | Refer for add-on treatment e.g. tiotropium,† anti-IgE, anti-IL5* |
| Other controller options | Consider low dose ICS                       | Leukotriene receptor antagonists (LTRA)<br>Low dose theophylline* | Med/high dose ICS<br>Low dose ICS+LTRA†<br>(or + theoph*) | Add tiotropium*<br>High dose ICS<br>+ LTRA<br>(or + theoph*) | Add low dose OCS                                                 |
| <b>RELIEVER</b>          | As-needed short-acting beta2-agonist (SABA) |                                                                   | As-needed SABA or low dose ICS/formoterol#                |                                                              |                                                                  |

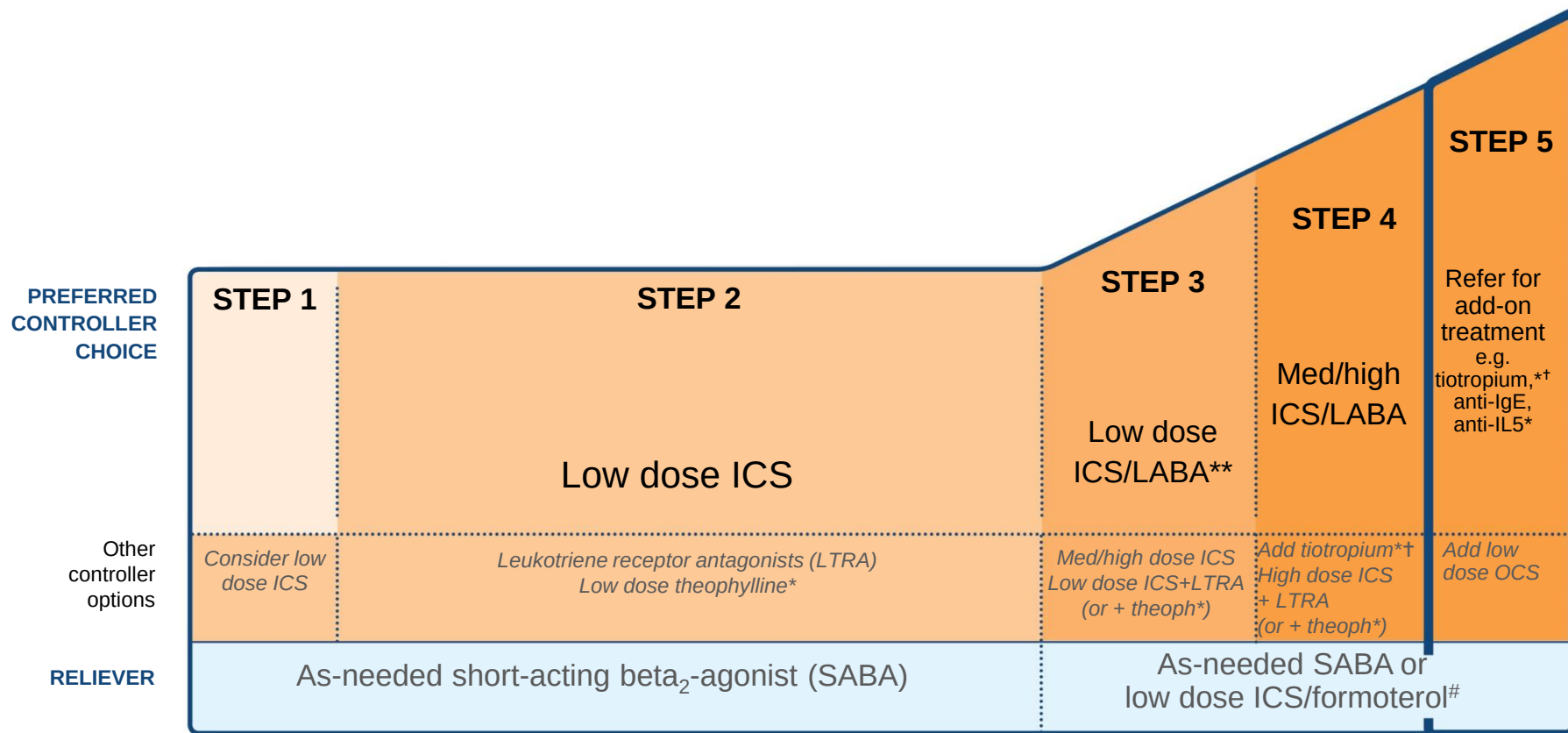
\*Not for children <12 years

\*\*For children 6-11 years, the preferred Step 3 treatment is medium dose ICS

#For patients prescribed BDP/formoterol or BUD/formoterol maintenance and reliever therapy

† Tiotropium by mist inhaler is an add-on treatment for patients ≥12 years with a history of exacerbations

# Step 5 – higher level care and/or add-on treatment



\*Not for children <12 years

\*\*For children 6-11 years, the preferred Step 3 treatment is medium dose ICS

#For patients prescribed BDP/formoterol or BUD/ formoterol maintenance and reliever therapy

† Tiotropium by mist inhaler is an add-on treatment for patients ≥12 years with a history of exacerbations

# Provide hands-on inhaler skills training



## Choose

- Choose an appropriate device before prescribing. Consider medication options, arthritis, patient skills and cost. For ICS by pMDI, prescribe a spacer
- Avoid multiple different inhaler types if possible



# Provide hands-on inhaler skills training



## Choose

- Choose an appropriate device before prescribing. Consider medication options, arthritis, patient skills and cost. For ICS by pMDI, prescribe a spacer
- Avoid multiple different inhaler types if possible

## Check

- Check technique at every opportunity – *“Can you show me how you use your inhaler at present?”*
- Identify errors with a device-specific checklist

## Correct

- Give a physical demonstration to show how to use the inhaler correctly
- Check again (up to 2-3 times)
- Re-check inhaler technique frequently, as errors often recur within 4-6 weeks

## Confirm

- Can you demonstrate correct technique for the inhalers you prescribe?
- Brief inhaler technique training improves asthma control

## Check adherence with asthma medications

- Poor adherence:
  - Is very common: it is estimated that 50% of adults and children do not take controller medications as prescribed
  - Contributes to uncontrolled asthma symptoms and risk of exacerbations and asthma-related death
- Contributory factors
  - Unintentional (e.g. forgetfulness, cost, confusion) and/or
  - Intentional (e.g. no perceived need, fear of side-effects, cultural issues, cost)
- How to identify patients with low adherence:
  - Ask an empathic question, e.g. *“Do you find it easier to remember your medication in the morning or the evening?”*, or *“Would you say you are taking it 3 days a week, or less, or more?”*
  - Check prescription date, label date and dose counter
  - Ask patient about their beliefs and concerns about the medication

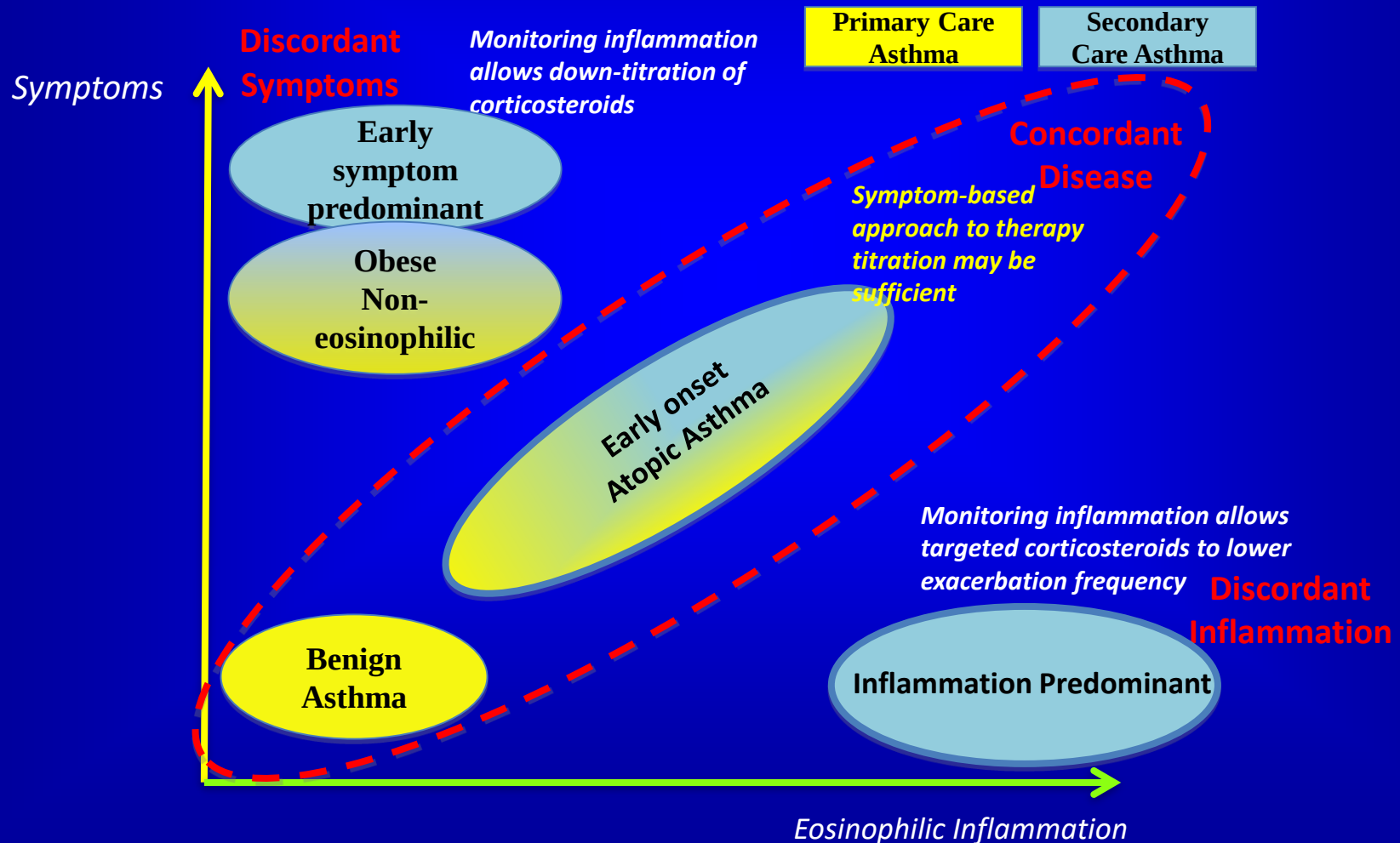
# Strategies to improve adherence in asthma

- Only a few interventions have been studied closely in asthma and found to be effective for improving adherence
  - Shared decision-making
  - Comprehensive asthma education with nurse home visits
  - Inhaler reminders for missed doses
  - Reviewing patients' detailed dispensing records

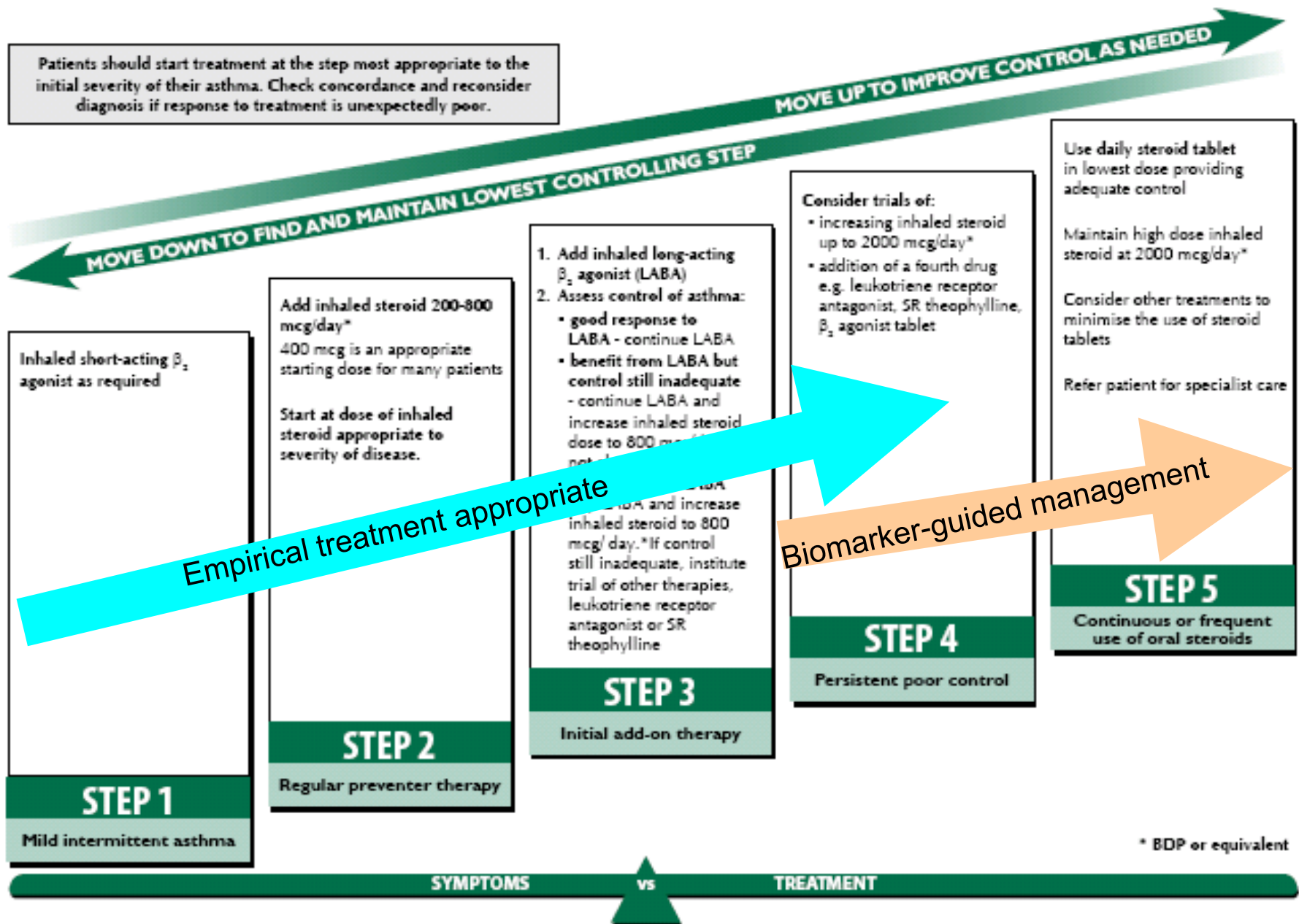
## ✓ Where is the need? Not in mild/moderate asthma

“A symptom based approach would be effective for mild to moderate asthma,... where concordance was observed between inflammation and symptoms”

Halder P, AJRCCM 2008



Patients should start treatment at the step most appropriate to the initial severity of their asthma. Check concordance and reconsider diagnosis if response to treatment is unexpectedly poor.



# ERS/ATS definition of severe asthma

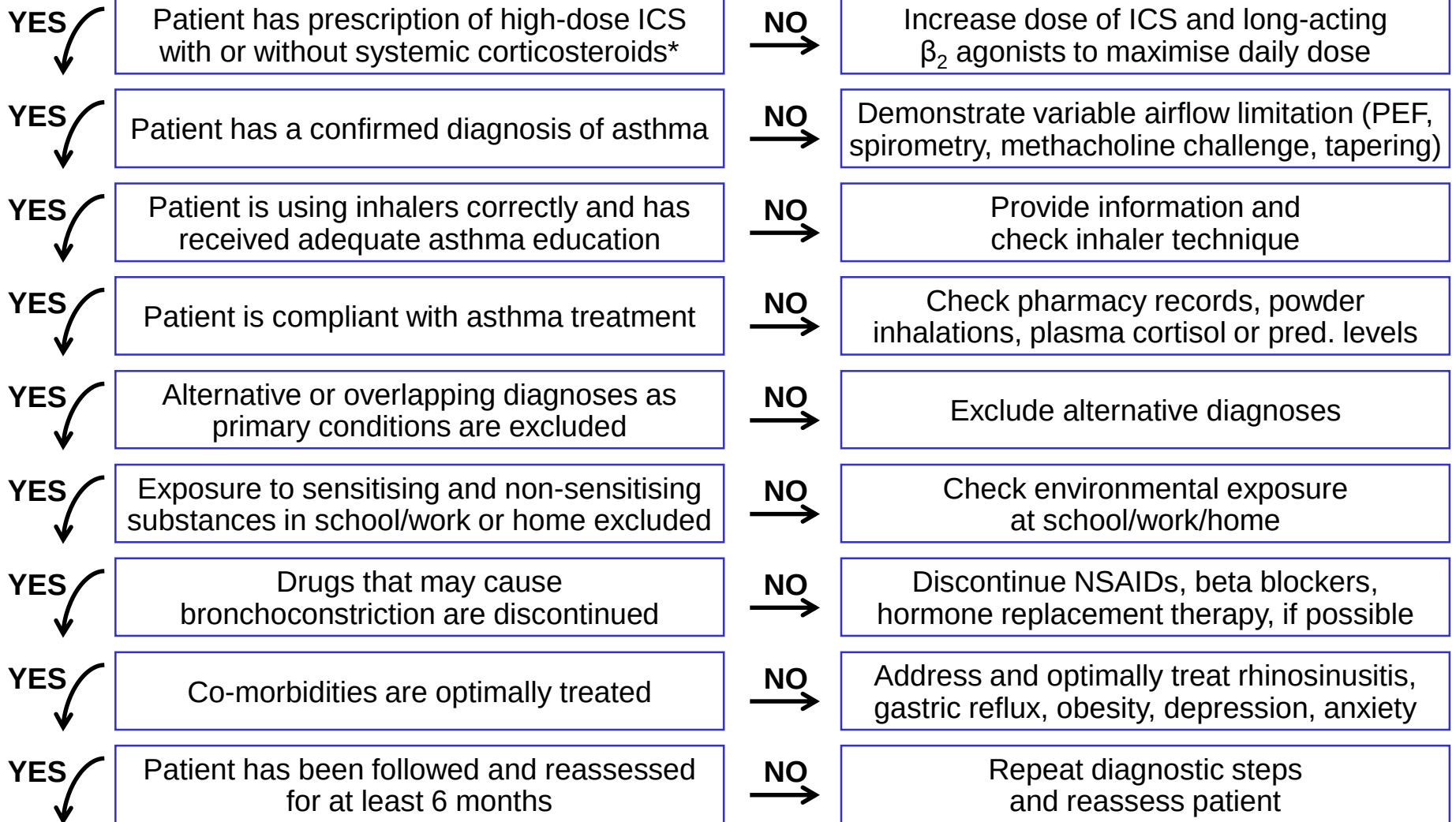
***‘Asthma which requires treatment with guidelines suggested medications for GINA steps 4–5 asthma (high-dose inhaled corticosteroids and long-acting  $\beta_2$ -agonists or leukotriene modifier/theophylline) for the previous year or systemic corticosteroids for  $\geq 50\%$  of the previous year to prevent it from becoming “uncontrolled” or which remains “uncontrolled” despite this therapy’***

# ERS/ATS definition of uncontrolled asthma

- A patient is deemed to have uncontrolled asthma if at least one of the following features is present:

|                              |                                      |
|------------------------------|--------------------------------------|
| <b>Poor symptom control</b>  | <b>Frequent severe exacerbations</b> |
| <b>Serious exacerbations</b> | <b>Airflow limitation</b>            |

Patient has uncontrolled asthma and/or frequent ( $\geq 2$ /year) exacerbations



➔ **Patient has severe refractory asthma**

\* 1,000 mcg/day fluticasone equivalent + long-acting  $\beta_2$  agonists or other controllers (adults). ICS = inhaled corticosteroids; NSAID = non-steroidal anti-inflammatory drug; PEF = peak expiratory flow. Bel EH et al. Thorax 2011;66:910-7.



# Factors to consider prior to a diagnosis of severe asthma

- Is asthma the true diagnosis?
  - Exclude differential diagnoses including COPD, vocal cord dysfunction, bronchiolitis (in children)
  - Complete pulmonary function tests, reversible airflow limitation
- Identification and avoidance / management of exacerbating factors and comorbidities
  - Full assessment for exacerbating factors including allergens, passive / active smoking, polyps
- Assessment of adherence and inhaler technique
  - Poor adherence and suboptimal inhaler technique are common in practice

- **Disease-related comorbidities**

*Rhinitis, rhinosinusitis +/- nasal polyposis* (and, in children, *rhinoconjunctivitis*) are the most frequent comorbidities and are often associated with uncontrolled asthma.

- **Comorbidities contributing to symptoms or poor quality of life**

*Obesity* may cause exertional dyspnoea by reducing the functional residual capacity and expiratory reserve volume. It may be associated in adults, particularly women, with refractory asthma

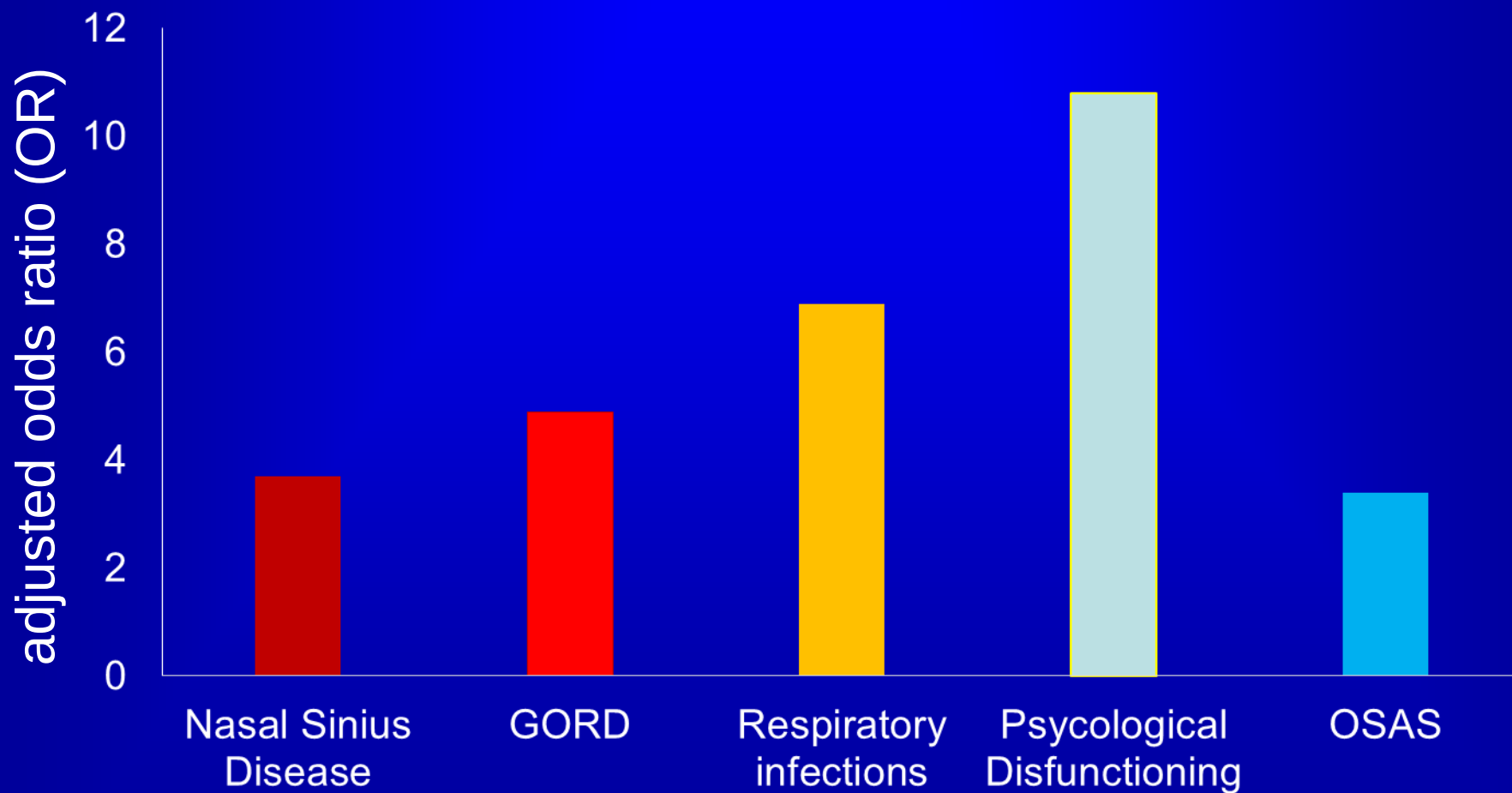
*Obstructive sleep apnoea (OSA)* is common among adults with asthma, particularly if severe.

*Gastro-oesophageal reflux disease (GORD)* is found in 25-80% of adults and children with asthma.

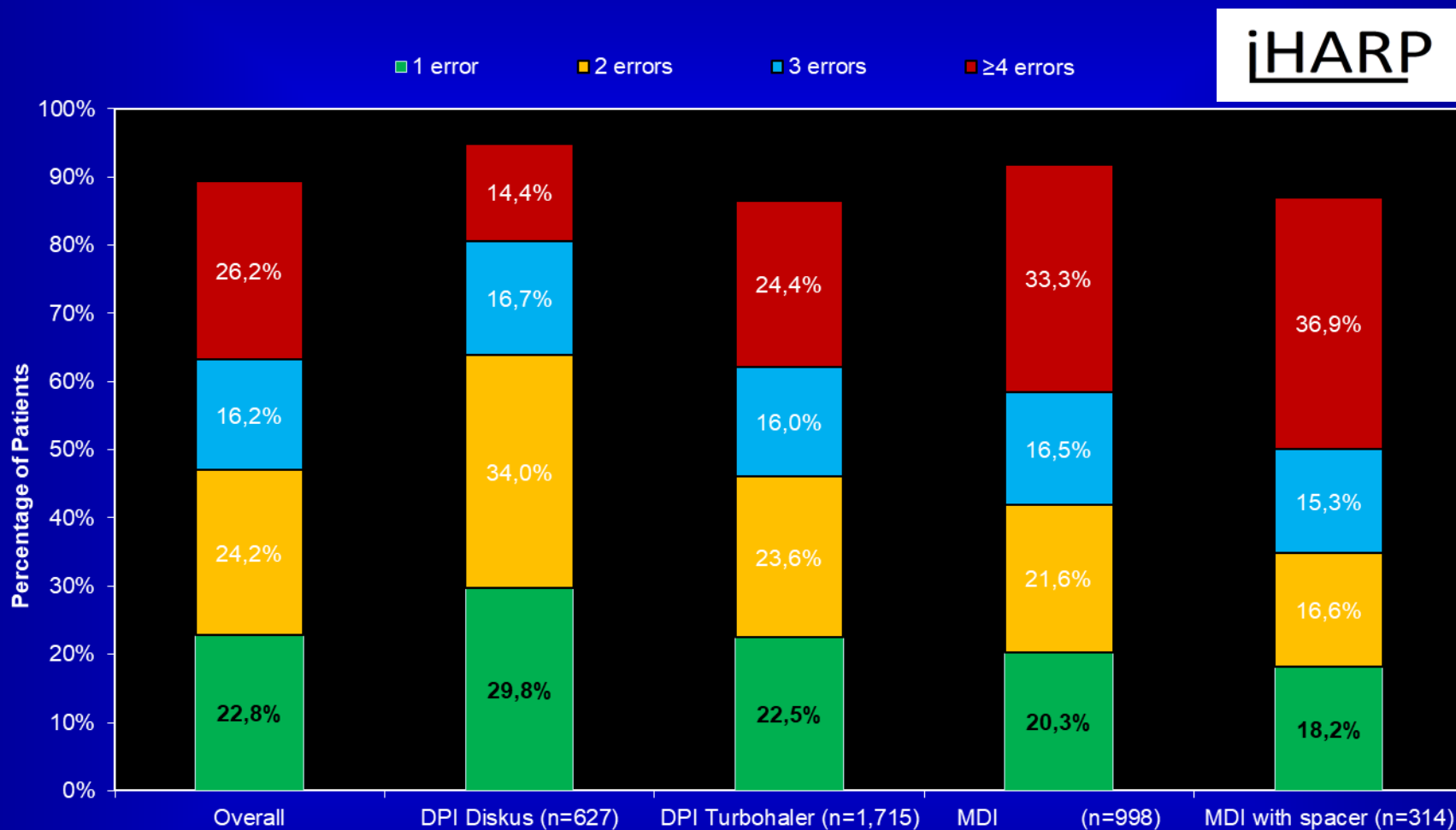
*Asthma–COPD overlap* is an interim term for adult patients with functional and clinical features of both asthma and COPD

*Mental disorders* (e.g., anxiety, depression, panic attacks) are more common in asthma of any severity, and impact on quality of life. Psychological stress may contribute to poor adherence, greater airway inflammation and worse asthma control.

# Exacerbations & difficult-to-treat asthma

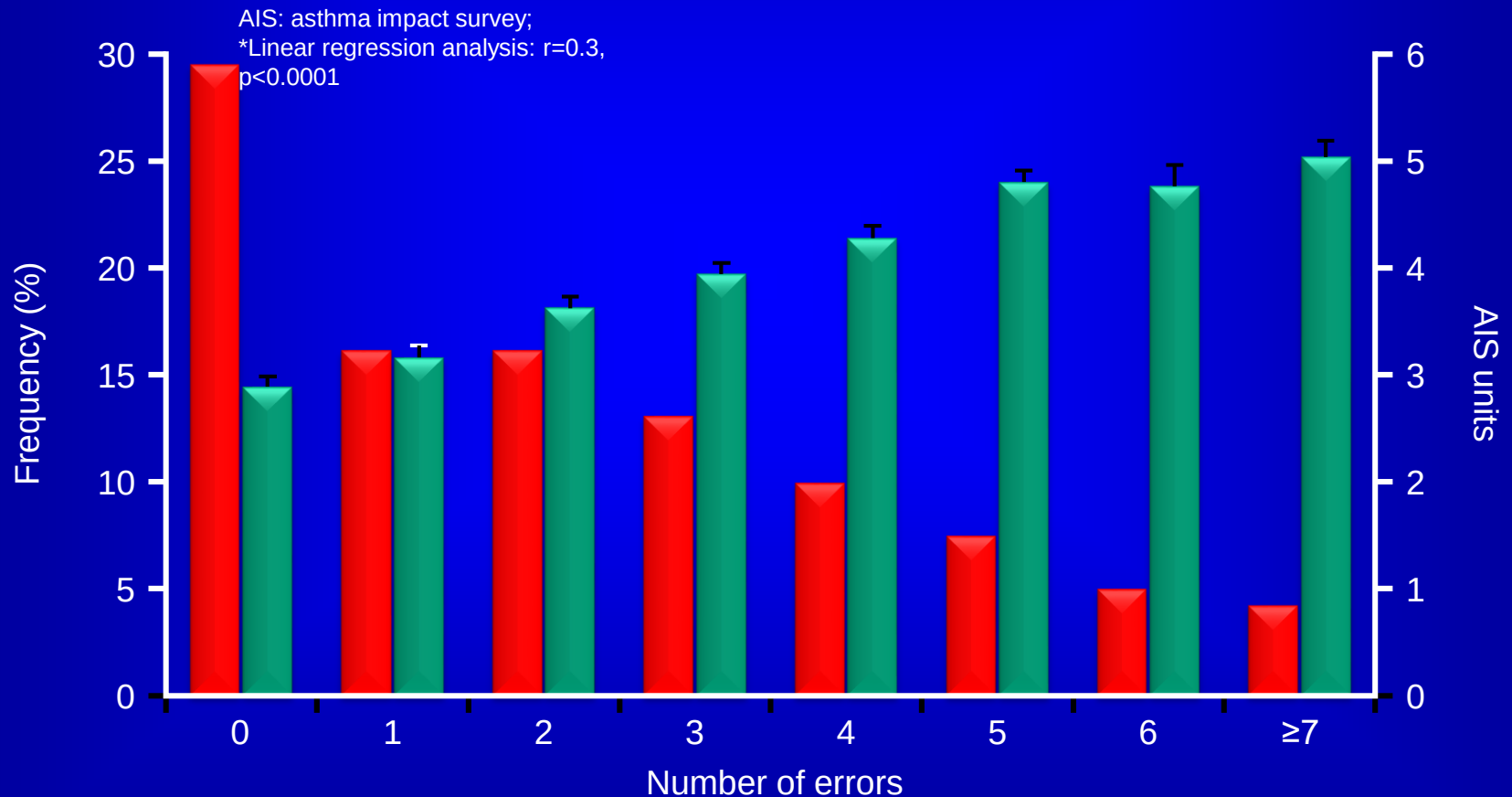


# More than 90% Patients make $\geq 1$ potentially serious inhaler error

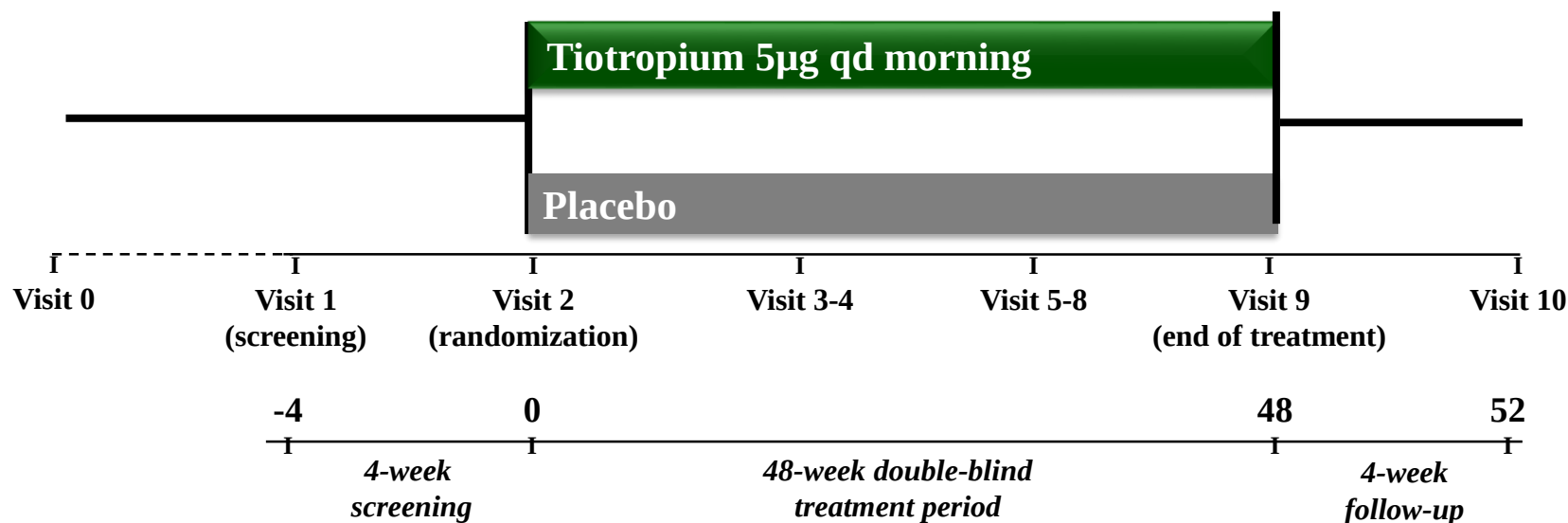


# Inhaler handling errors are related to poorer asthma stability

- Frequency distribution of the number of errors in inhalation technique (left axis)
- Relationship\* between number of errors and AIS (right axis)



Study design: double-blind, randomized, placebo-controlled, parallel-group (two identical trials)



### Three coprimary endpoints:

FEV<sub>1</sub> peak  
(0-3 h) after 24  
weeks

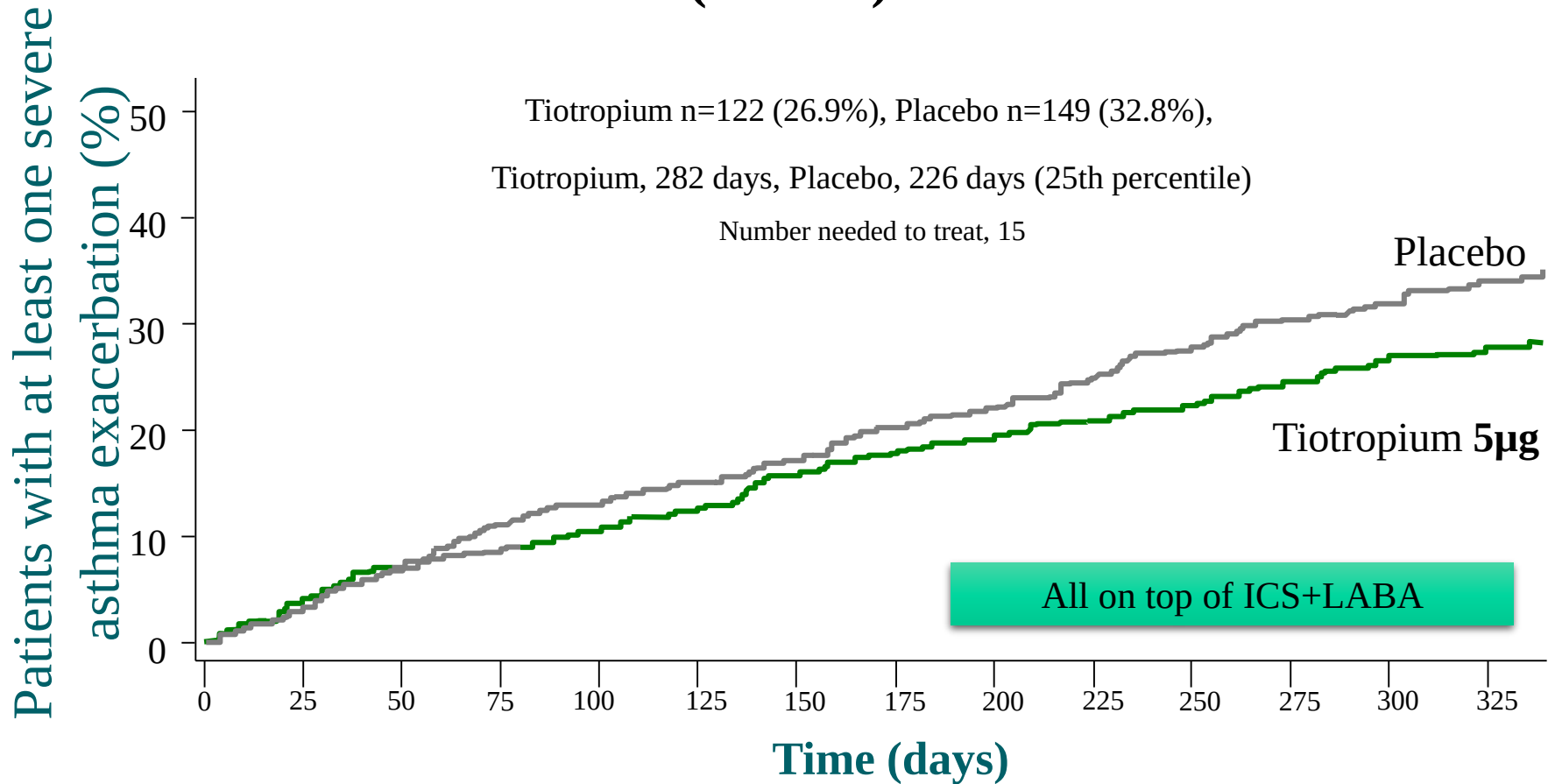
FEV<sub>1</sub> trough  
after 24 weeks

Time to first severe asthma  
exacerbation in pooled  
analysis after 48 weeks

All patients at least on ICS  
maintenance therapy  
(≥800µg budesonide or  
equivalent/day)+LABA

117 centres, 5 continents

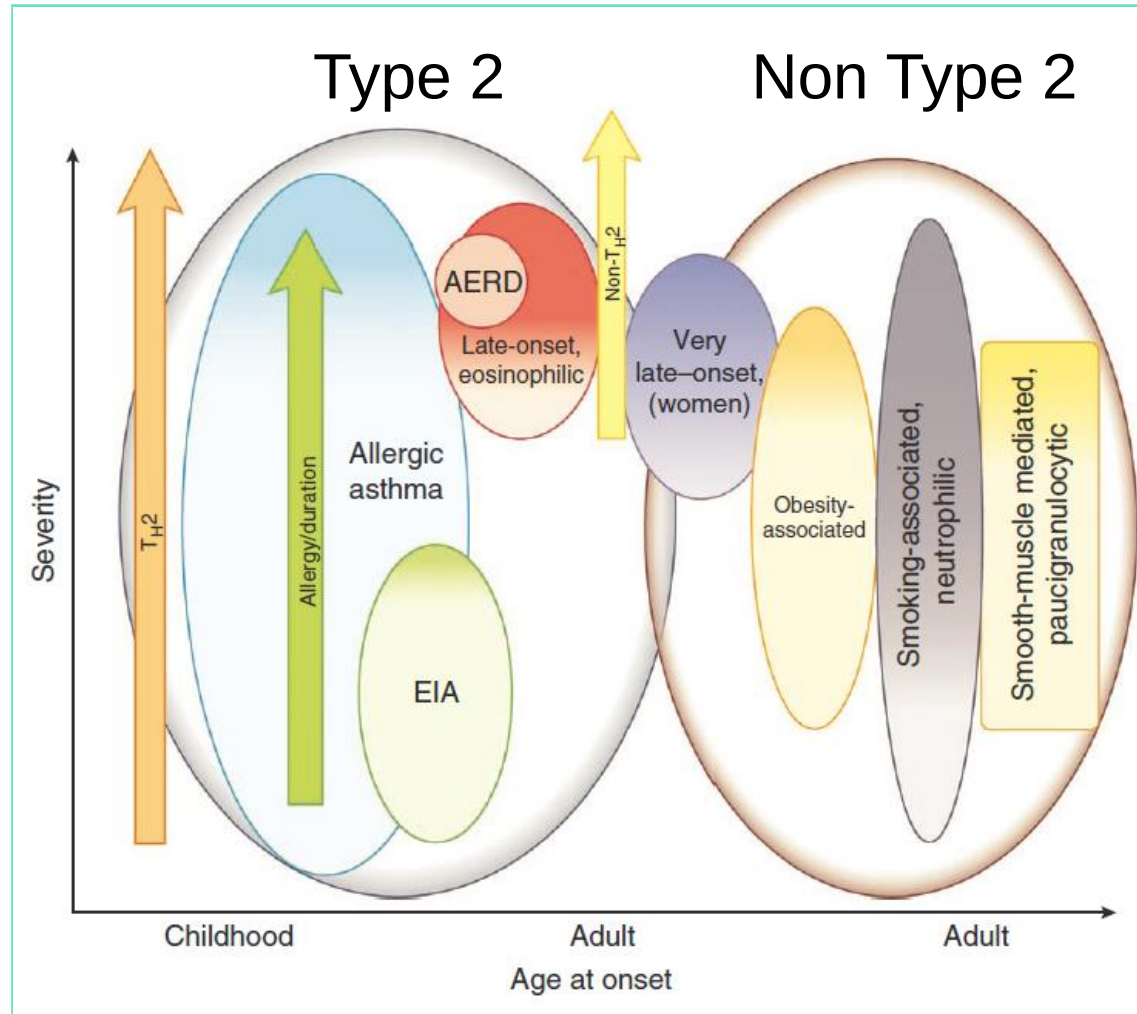
**HR=0.79; Risk reduction of 21%  
(*P*=0.03)**



Patients at risk

|                |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|----------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Placebo        | 454 | 435 | 412 | 388 | 379 | 367 | 356 | 339 | 332 | 319 | 303 | 290 | 282 | 272 |
| Tiotropium 5µg | 453 | 430 | 409 | 401 | 389 | 378 | 363 | 353 | 348 | 339 | 331 | 319 | 308 | 298 |

# THEORETICAL GROUPING OF EMERGING ASTHMA PHENOTYPES BASED ON THE DISTINCTION BETWEEN TH2-HIGH ASTHMA AND NON-TH2 ASTHMA

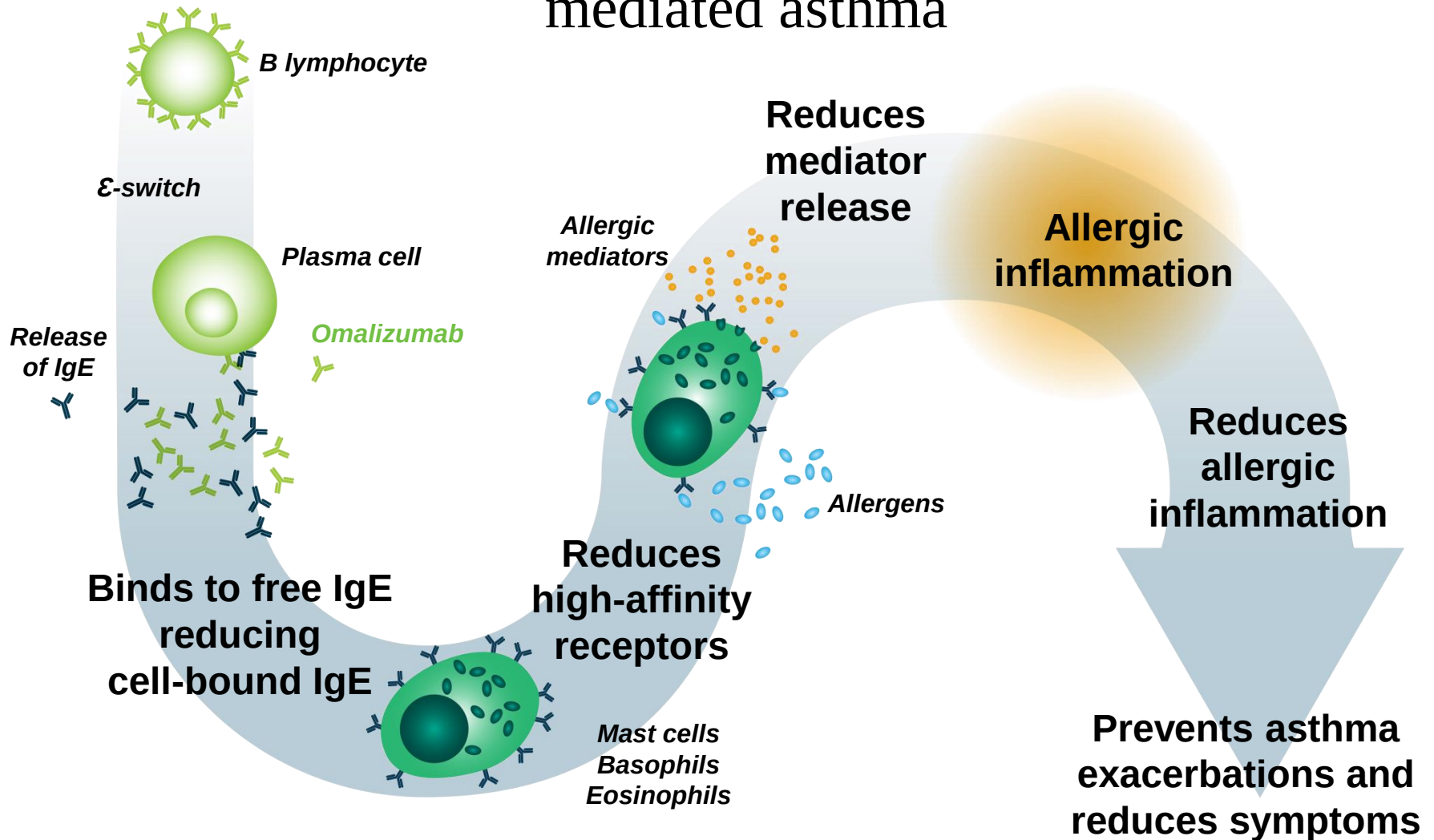




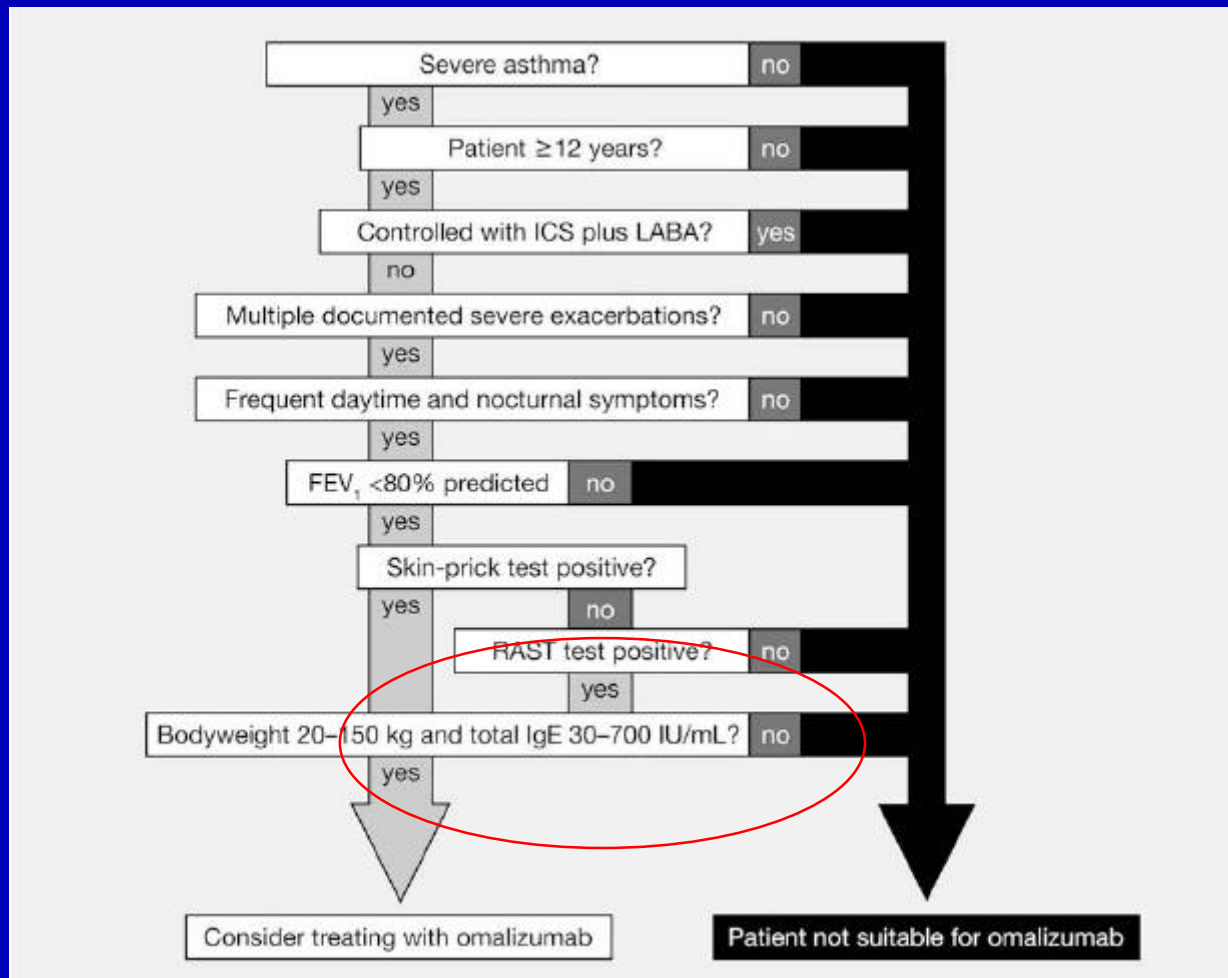
## Biological Drugs in asthma treatment

| Drug         | Mechanism of action                                     | Effects                                                                                               | Development*             |
|--------------|---------------------------------------------------------|-------------------------------------------------------------------------------------------------------|--------------------------|
| Omalizumab   | Binds free IgE                                          | Reduces exacerbations, improves symptoms and quality of life                                          | FDA- and EMA-approved    |
| Mepolizumab  | Blocks IL-5                                             | Decreases the number of eosinophils and frequency of exacerbations, as well as prednisone consumption | Phase II/III             |
| Reslizumab   | Blocks IL-5                                             | Decreases the number of sputum eosinophils and enhances FEV1                                          | Phase II                 |
| Benralizumab | Inhibits binding of IL-5 to IL-5R $\alpha$              | Depletes the number of peripheral blood eosinophils                                                   | Phase I/II               |
| Pascolizumab | Blocks IL-4                                             | No significant clinical efficacy                                                                      | Phase II                 |
| Altrakincept | Soluble IL-4R                                           | No significant clinical efficacy                                                                      | Phase II                 |
| Pitrakinra   | Inhibits binding of IL-4 and/or IL-13 to IL-4R $\alpha$ | May prevent a decrease in FEV1 after allergen challenge                                               | Phase II                 |
| Tralokinumab | Blocks IL-13                                            | Reduces airway eosinophilia                                                                           | Phase I/II               |
| Anrukinzumab | Blocks IL-13                                            | Inhibits allergen-induced late-phase asthmatic responses                                              | Phase II                 |
| Lebrikizumab | Blocks IL-13                                            | Enhances FEV1 in patients with high serum levels of periostin                                         | Phase II                 |
| MEDI-528     | Blocks IL-9                                             | Reduces airway inflammation and hyper-responsiveness in mice                                          | Phase II                 |
| MT203        | Blocks GM-CSF                                           | Decreases survival and activation of eosinophils                                                      | Phase II                 |
| Secukinumab  | Blocks IL-17                                            | Data not yet available                                                                                | Phase II;<br>NCT01478360 |
| Golimumab    | Blocks TNF $\alpha$                                     | May increase the risk of infections and malignancies                                                  | Suspended                |
| Infliximab   | Blocks TNF $\alpha$                                     | Reduces PEF oscillations and asthma exacerbations                                                     | Phase II                 |
| Etanercept   | Soluble TNF $\alpha$ receptor                           | Conflicting data; see main text                                                                       | Phase II                 |

# Omalizumab prevents the allergic cascade in IgE-mediated asthma



The Wave of Personalized Medicine in asthma  
*“Biomarker-Driven Therapy Is Ready for the Clinic”*



The use of Omalizumab in the treatment of severe allergic asthma.  
Holgate ST, Resp Med 2009

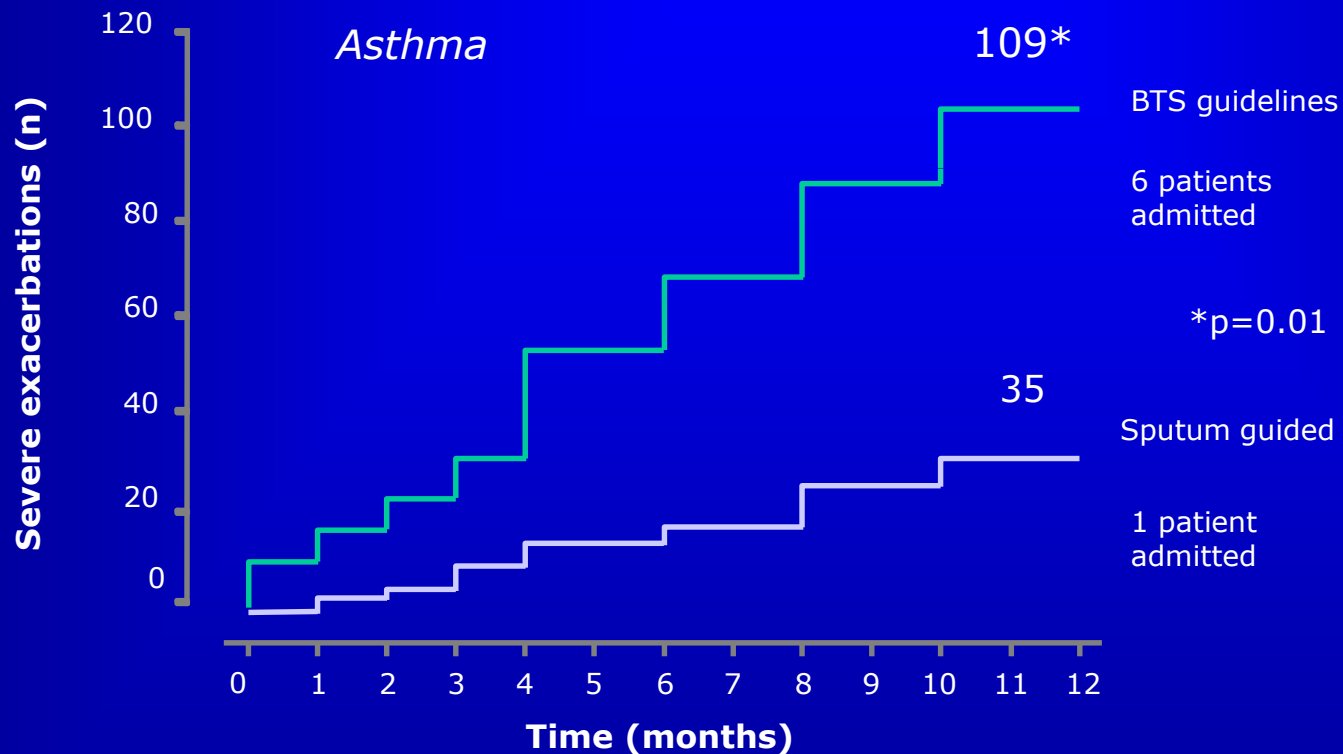
# Therapeutic antibodies entered clinical development

- Cytokines released by immune-inflammatory and airway structural cells contribute to asthma inflammation<sup>1</sup>
- Research has identified several potential cytokine targets for anti-asthma therapy<sup>2–4</sup>

| Therapeutic antibody | Target        |  | Therapeutic antibody   | Target       |
|----------------------|---------------|--|------------------------|--------------|
| Infliximab           | TNF- $\alpha$ |  | Mepolizumab            | IL-5         |
| Golimumab            | TNF- $\alpha$ |  | Benralizumab           | IL-5R        |
| Etanercept           | TNF- $\alpha$ |  | Reslizumab             | IL-5         |
| Daclizumab           | IL-2R (CD25)  |  | QAX576 <sup>4</sup>    | IL-13        |
| Secukinumab          | IL-17A        |  | Tralokinumab           | IL-13        |
| Brodalumab           | IL-17         |  | Lebrikizumab           | IL-13        |
|                      |               |  | Dupilumab <sup>4</sup> | IL-4R/IL-13R |

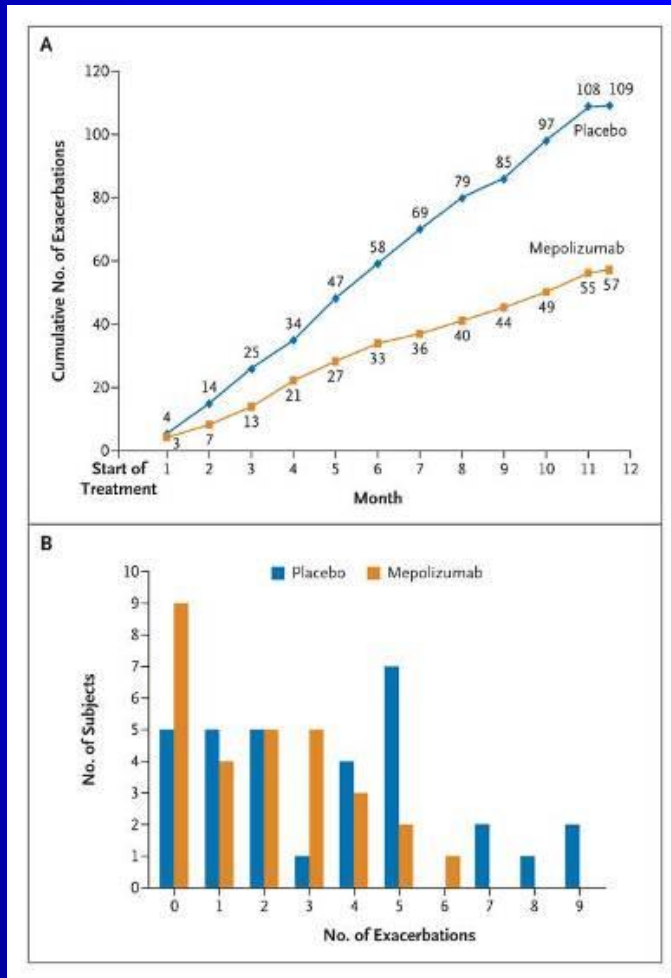
1. Lambrecht BN & Hammad H. *Nat Immunol* 2015; 16:45–56; 2. Gallelli L, et al. *Biomed Res Int* 2013; 2013:104315;  
3. Menzella F, et al. *Multidiscip Respir Med* 2015;10:1; 4. <https://clinicaltrials.gov/ct2/home>.

## Targeting sputum eosinophilia and severe exacerbations of asthma

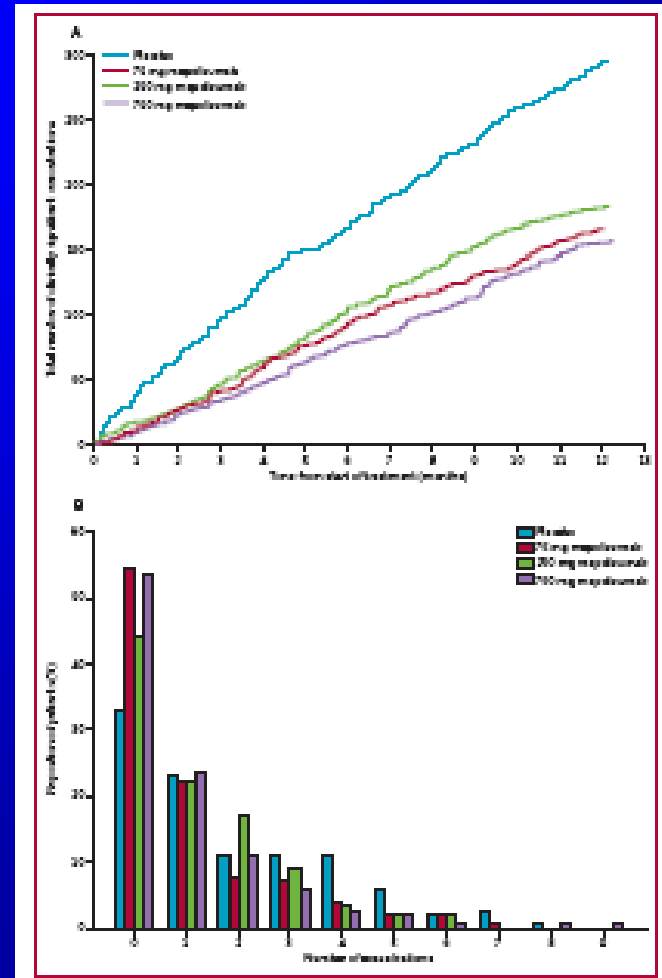


Green et al, Lancet 2002; 360: 1715-21

# Mepolizumab: effect on severe exacerbations

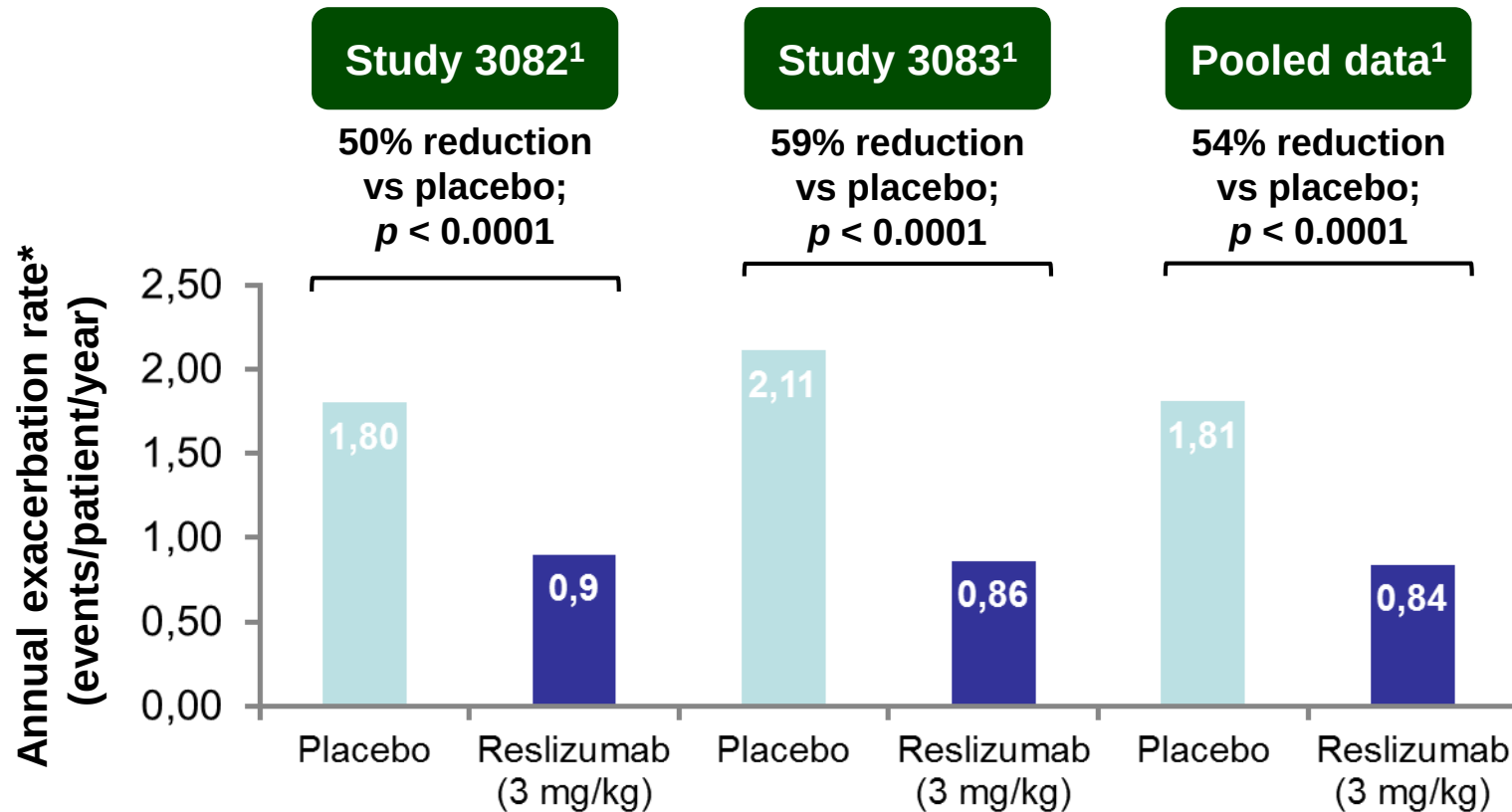


Haldar et al. NEJM 2009;360:973-84



Pavord et al. Lancet 2012;380:651-9.

# Studies 3082 and 3083: Reslizumab consistently reduced clinical exacerbation rates compared with placebo



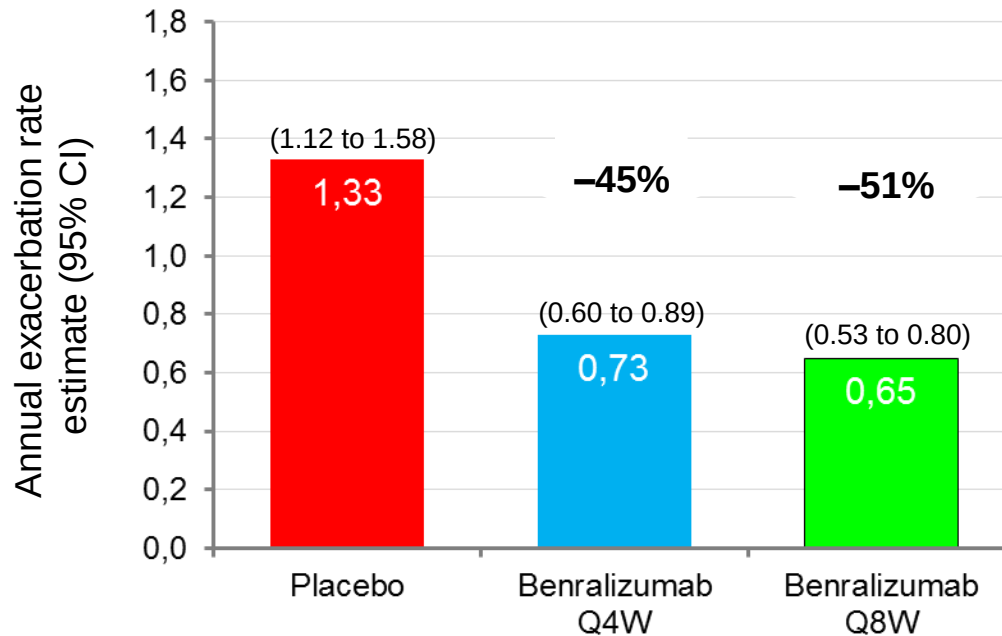
**Reslizumab significantly reduced the annual exacerbation rate in patients with inadequately controlled asthma and active eosinophilic airway inflammation<sup>1</sup>**

\* Exacerbations were defined as worsening asthma resulting in any of the following: use of systemic corticosteroids in steroid-naïve patients, a two-fold increase in the dose of either ICS or systemic corticosteroids for  $\geq 3$  days, the need for asthma-related emergency treatment.

1. Castro M, et al. *Lancet Respir Med* 2015; 3:355–366.

# Annual asthma exacerbation rate reduction with benralizumab

Blood eosinophils  $\geq 300$  cells/ $\mu$ L<sup>a</sup>



Annual exacerbation rate ratio vs. placebo<sup>b</sup>

**Q4W**

0.55 (0.42 to 0.71)  
 $p < 0.0001$

**Q8W**

0.49 (0.37 to 0.64)  
 $p < 0.0001$

<sup>a</sup>Adolescents represented 4%, 3%, and 4% of the placebo, Q4W, and Q8W cohorts, respectively.

<sup>b</sup>Estimates calculated by a negative binomial model with adjustment for treatment, region, oral corticosteroid use, and prior exacerbations.  
95% CI: confidence interval.



## Profile: Anti-IL 5 treatments

- The magnitude of benefit for exacerbation reduction is greater in individuals with a higher number of exacerbations in the previous year and higher blood eosinophil counts. However, improvements, especially in symptoms, remain slight.
- Mepolizumab and Benralizumab also enabled prednisolone-dependent people with asthma to successfully withdraw oral corticosteroid treatment.
- Antiinterleukin- 5 receptor strategies have successfully identified a target group, patients with eosinophilic inflammation, and an important outcome, exacerbation reduction.
- Phase 3 trials demonstrated similar reductions in exacerbation frequency with modest effects on lung function and asthma control..

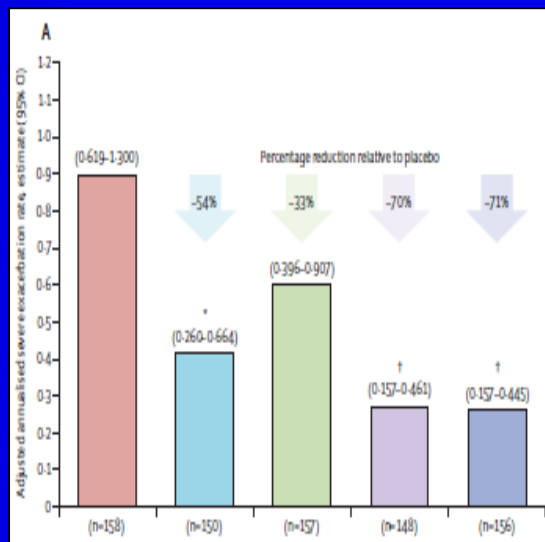
# ADJUSTED ANNUALISED SEVERE EXACERBATION EVENT RATES ESTIMATED FROM THE 24-WEEK TREATMENT PERIOD

769 severe asthmatics  
not controlled by inhaled  
LABA/highICS

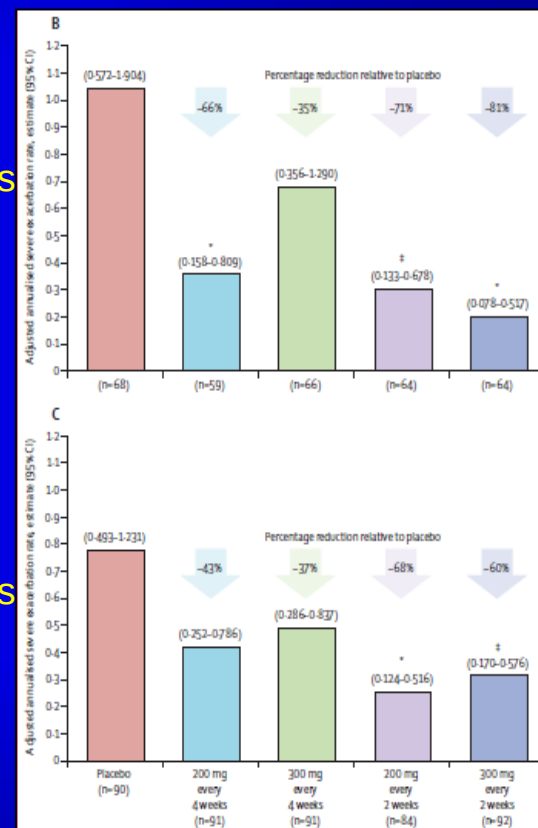
Treated with dupilumab  
200-300 mg sc every 2 or  
4 weeks for 12 months

Powered on FEV1

Dupilumab improves  
lung functions and  
reduces severe  
exacerbations  
irrespective of baseline  
eosinophil count

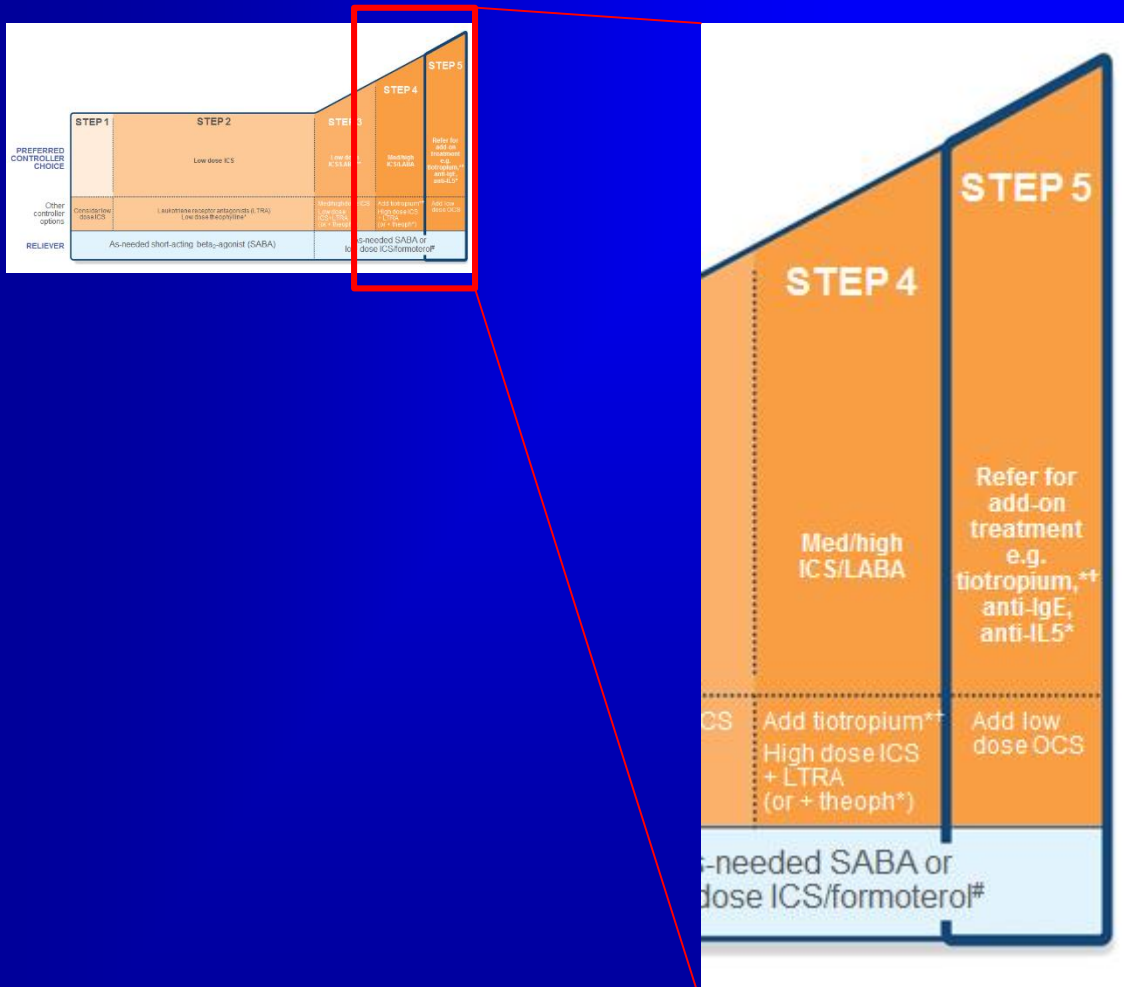


Blood Eos  
>300/uL



Blood Eos  
<300/uL

# Impact on the treatment pathway «TYPE 2»



Fevipiprant – CRTH2 antagonist  
Before any mABs?  
Intermittent: viral – seasonal?

Dupilumab  
Not only exacerbations  
High + low eos?  
Comorbidities

Tralokinumab ?  
High Periostin/DPP4?

Anti TSLP ?  
Intermittent - seasonal

Azithromycin?  
Treatment for the poor?

# Definition and terminology

- A flare-up or exacerbation is an acute or sub-acute worsening of symptoms and lung function compared with the patient's usual status
- Terminology
  - 'Flare-up' is the preferred term for discussion with patients
  - 'Exacerbation' is a difficult term for patients
  - 'Attack' has highly variable meanings for patients and clinicians
  - 'Episode' does not convey clinical urgency
- Consider management of worsening asthma as a continuum
  - Self-management with a written asthma action plan
  - Management in primary care
  - Management in the emergency department and hospital
  - Follow-up after any exacerbation

# Identify patients at risk of asthma-related death

- Patients at increased risk of asthma-related death should be identified
  - Any history of near-fatal asthma requiring intubation and ventilation
  - Hospitalization or emergency care for asthma in last 12 months
  - Not currently using ICS, or poor adherence with ICS
  - Currently using or recently stopped using OCS
    - (indicating the severity of recent events)
  - Over-use of SABAs, especially if more than 1 canister/month
  - Lack of a written asthma action plan
  - History of psychiatric disease or psychosocial problems
  - Confirmed food allergy in a patient with asthma
- Flag these patients for more frequent review

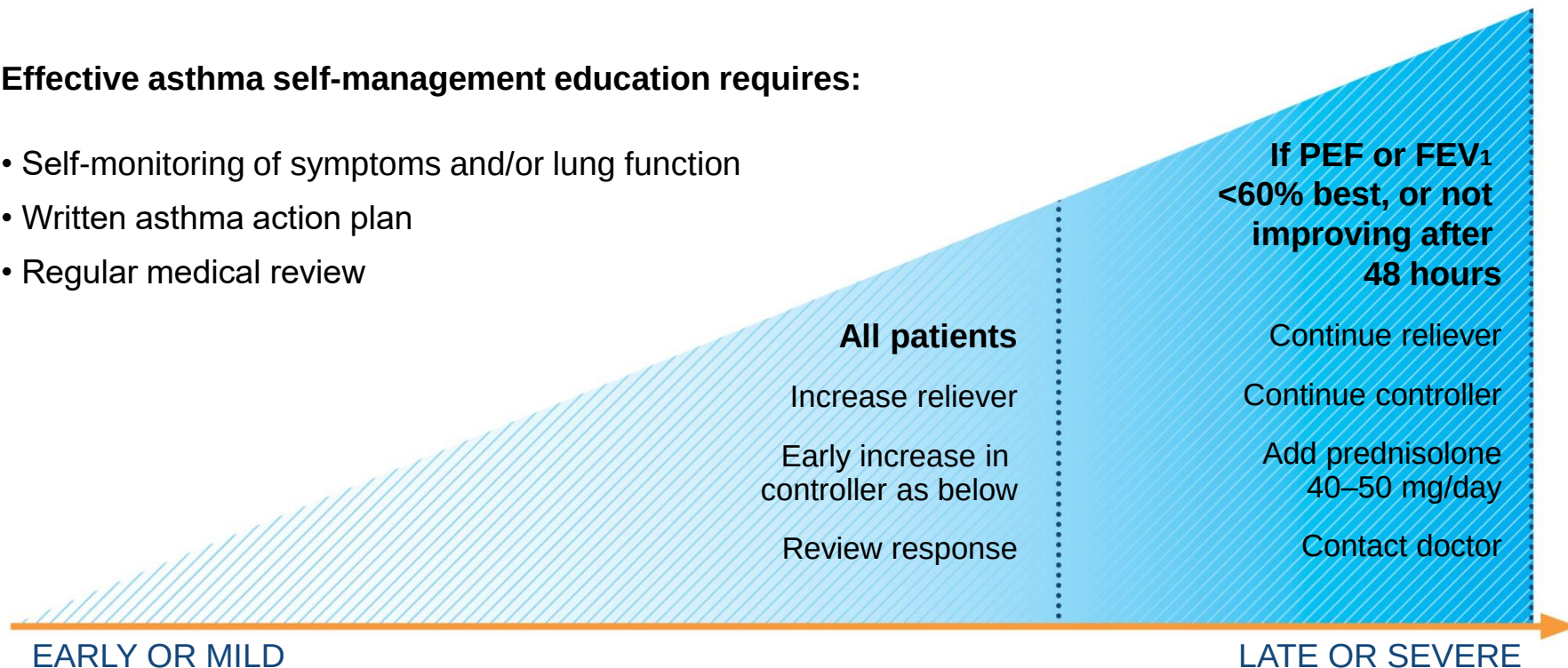
# Written asthma action plans

- All patients should have a written asthma action plan
  - The aim is to show the patient how to recognize and respond to worsening asthma
  - It should be individualized for the patient's medications, level of asthma control and health literacy
  - Based on symptoms and/or PEF (children: only symptoms)
- The action plan should include:
  - The patient's usual asthma medications
  - When/how to increase reliever and controller or start OCS
  - How to access medical care if symptoms fail to respond
- Why?
  - When combined with self-monitoring and regular medical review, action plans are highly effective in reducing asthma mortality and morbidity

# Written asthma action plans

## Effective asthma self-management education requires:

- Self-monitoring of symptoms and/or lung function
- Written asthma action plan
- Regular medical review



# Management of asthma exacerbations in primary care

- 1 - Reassess diagnosis: Asthma? (see clinical presentation)
- 2 - Check for risk factors for asthma related death (see clinical assessment of asthma exacerbations)

## 3 - Triage

|                           |                                                                                   |                                                                                                                            |                                                                                                                      |                                                                                                                             |
|---------------------------|-----------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|
| POSITION                  |  |  prefers sitting to lying<br>NOT AGITATED |  sits hunched forward<br>AGITATED |  sits hunched forward<br>DROWSY/CONFUSED |
| SPEECH                    |  | phrases                                                                                                                    | words                                                                                                                | confused                                                                                                                    |
| RESP. RATE                |  | < 30                                                                                                                       | > 30                                                                                                                 | > 30                                                                                                                        |
| HEART RATE                |  | 100-120                                                                                                                    | > 120                                                                                                                | > 120                                                                                                                       |
| O <sub>2</sub> SATURATION |  | ≥ 90%                                                                                                                      | < 90%                                                                                                                | < 90%                                                                                                                       |
| AUSCULTATION              |  | wheeze                                                                                                                     | wheeze                                                                                                               | silent chest                                                                                                                |
| PEF                       |  | > 50% pred or best                                                                                                         | ≤ 50% pred or best                                                                                                   | -                                                                                                                           |
|                           |                                                                                   | MILD MODERATE                                                                                                              | SEVERE                                                                                                               | LIFE THREATENING                                                                                                            |

**START TREATMENT**

- SABA 4-10 puffs (pMDI+spacer)  
Every 20 min for 1h
- Prednisolone: Adults 1 mg/Kg, max 50 mg, child 1-2 mg/Kg, max 40 mg
- O<sub>2</sub>: target SO<sub>2</sub> 93-95% (child. 94-98%)

REVIEW FREQUENTLY. MEASURE LUNG FUNCTION AFTER 1 HOUR.

**TRANSFER urgently to ACUTE CARE FACILITY**

Start treatment while waiting:

- SABAs+ipratropium bromide
- O<sub>2</sub>
- Systemic corticosteroid

|                           |                                                                                            |                                              |                                                 |
|---------------------------|--------------------------------------------------------------------------------------------|----------------------------------------------|-------------------------------------------------|
| SYMPTOMS                  |  WHEEZE | IMPROVED                                     | NOT IMPROVED OR WORSENING                       |
| O <sub>2</sub> SATURATION |         | > 94% ROOM AIR                               | ≤ 94% ROOM AIR                                  |
| PEF                       |         | IMPROVING AND >60-80% PRED. OR PERSONAL BEST | NOT IMPROVING AND <60-80% PRED. / PERSONAL BEST |
| HOME RESOURCES            |         | ADEQUATE                                     | INADEQUATE                                      |

## Arrange at discharge

Reliever as needed. Instruct about tapering SABA  
Controller start or step up; check technique+adherence  
Prednisolone continue for 5-7 days (child 3-5)  
Give interim action plan  
Follow up within 2-7 days



# Exacerbation management in acute care facility, e.g. emergency department

