

# Supplementary Materials

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| <b>Supplementary Table S1 – ICD-10 and ATC codes</b> |                                                                                                         |                                         |
|------------------------------------------------------|---------------------------------------------------------------------------------------------------------|-----------------------------------------|
| <b>Criteria</b>                                      |                                                                                                         | <b>ICD-10 or ATC code</b>               |
| <b>Inclusion criteria</b>                            |                                                                                                         |                                         |
| Diagnosis code for bronchiectasis                    | DJ47                                                                                                    |                                         |
| <b>Exclusion criteria</b>                            |                                                                                                         |                                         |
| Cystic fibrosis                                      | DE84, DQ33                                                                                              |                                         |
| Malignant neoplasm                                   | DC00-DC97                                                                                               |                                         |
| Immunodeficiency                                     | DD80-84, DD85, DD89                                                                                     |                                         |
| Disease-modifying anti-rheumatic drugs               | L04AX03, L01AA01, A07EC01, L04AD01, L04AA13, L04AX01, L04AA06, P01BA02                                  |                                         |
| <b>Age/Comorbidities</b>                             |                                                                                                         | <b>Weight for CCI score calculation</b> |
| Age 50-59                                            |                                                                                                         | +1                                      |
| Age 60-69                                            |                                                                                                         | +2                                      |
| Age 70-79                                            |                                                                                                         | +3                                      |
| Age >80                                              |                                                                                                         | +4                                      |
| Heart failure                                        | DI50, DI11.0, DI13.0, DI13.2                                                                            | +1                                      |
| Myocardial infarction                                | DI21, DI22, DI23                                                                                        | +1                                      |
| Peripheral vascular disease                          | DI70, DI71, DI72, DI73, DI74, DI77                                                                      | +1                                      |
| Cerebrovascular disease                              | DI60-69, DG45, DG46                                                                                     | +1                                      |
| Dementia                                             | DF00-03, DF05.1, DG30                                                                                   | +1                                      |
| COPD/asthma                                          | DJ40-47, DJ60-67, DJ68.4, DJ70.1, DJ70.3, DJ84.1, DJ92.0, DJ96.1, DJ98.2, DJ98.3<br>Or ATC R03BB, R03AL | +1                                      |
| Connective tissue disease                            | DM05, DM06, DM08, DM09, DM30-36, DD86                                                                   | +1                                      |
| Ulcer disease                                        | DK21.1, DK25-28                                                                                         | +1                                      |
| Hemiplegia/paraplegia                                | DG81, DG82                                                                                              | +2                                      |
| Diabetes mellitus                                    | DE10.0, DE10.1, DE10.9, DE11.0, DE11.1, DE11.9                                                          | +1                                      |
| Diabetes mellitus with chronic complications         | DE10.2-10.8, DE11.2-11.8                                                                                | +2                                      |
| Mild liver disease                                   | DB18, DK70.1, DK70.2, DK70.3, DK70.9, DK71, DK73, DK74, DK76                                            | +1                                      |
| Moderate/severe liver disease                        | DB15.0, DB16.0, DB16.2, DB19.0, DK70.4, DK72, DK76.6, DI85                                              | +3                                      |
| Moderate/severe renal disease                        | DI12, DI13, DN00-05, DN07, DN11, DN14, DN17-19, DQ61                                                    | +2                                      |
| AIDS                                                 | DB21-24                                                                                                 | +6                                      |
| <b>Treatments</b>                                    |                                                                                                         |                                         |
| Antibiotics                                          | J01CE02, J01CA04, J01CR02, J01FA01, J01FA09, J01FA06, J01FA10, J01MA02, J01MA14, J01AA02                |                                         |
| LABA                                                 | R03AC                                                                                                   |                                         |

|     |                  |
|-----|------------------|
| OCS | H02AB06, H02AB07 |
|-----|------------------|

*Supplementary Table S1 – ICD-10 and ATC-codes used in the study. All comorbidities are within five years before cohort entry, and all treatments are within 365 days before cohort entry. ICD-10: International Classification of Diseases, 10<sup>th</sup> edition. ATC: Anatomic Therapeutic Chemical Classification. CCI: Charlson Comorbidity Index. COPD: Chronic obstructive pulmonary disease. AIDS: Acquired Immunodeficiency Syndrome. LABA: Long-acting beta agonist. OCS: Oral corticosteroid.*

| Supplementary Table S2 - Number of patients in ICS exposure groups 365 days before and after BE diagnosis |              |              |                   |               |             |
|-----------------------------------------------------------------------------------------------------------|--------------|--------------|-------------------|---------------|-------------|
| ICS exposure group                                                                                        | No ICS       | Low-dose ICS | Moderate-dose ICS | High-dose ICS | Total       |
| <b>Prior to BE diagnosis, n (%)</b>                                                                       | 3,003 (59.0) | 970 (19.0)   | 596 (11.7)        | 524 (10.3)    | 5,093 (100) |
| <b>Following BE diagnosis, n (%)</b>                                                                      | 2,996 (58.8) | 935 (18.4)   | 622 (12.2)        | 540 (10.6)    | 5,093 (100) |

*Supplementary Table S2 - Number of patients categorized by ICS exposure 365 days prior to and following BE diagnosis: no ICS group or stratified into a low-dose ( $\leq 400$   $\mu\text{g/day}$ ), moderate-dose (401-999  $\mu\text{g/day}$ ) and high-dose ( $\geq 1,000$   $\mu\text{g/day}$ ) ICS exposure group. ICS: inhaled corticosteroids. BE: Non-cystic fibrosis bronchiectasis*

| <b>Supplementary Table S3 - Numbers of patients in ICS exposure groups at cohort entry and 90 days prior to first-time <i>S. aureus</i> isolation</b> |               |                     |                          |                      |              |
|-------------------------------------------------------------------------------------------------------------------------------------------------------|---------------|---------------------|--------------------------|----------------------|--------------|
| <b>ICS exposure group</b>                                                                                                                             | <b>No ICS</b> | <b>Low-dose ICS</b> | <b>Moderate-dose ICS</b> | <b>High-dose ICS</b> | <b>Total</b> |
| <b>At cohort entry, n (%)</b>                                                                                                                         | 69 (44.2)     | 26 (16.7)           | 17 (10.9)                | 44 (28.2)            | 156 (100)    |
| <b>90 days prior to first-time <i>S. aureus</i> isolation, n (%)</b>                                                                                  | 91 (58.3)     | 43 (27.6)           | 20 (12.8)                | 2 (1.3)              | 156 (100)    |

Supplementary Table S3 - Numbers of patients categorized into ICS exposure groups at cohort entry and 90 days prior to first-time *S. aureus* isolation. Low-dose ICS  $\leq 400$  ug/day, moderate-dose ICS 401-999 ug/day, high-dose ICS  $\geq 1000$  ug/day. ICS: Inhaled corticosteroids. *S. aureus*: *Staphylococcus aureus*.

| <b>Supplementary Table S4 - Cause-specific Cox proportional hazards regression results with adjusted confounders</b> |      |            |         |
|----------------------------------------------------------------------------------------------------------------------|------|------------|---------|
|                                                                                                                      | HR   | 95% CI     | P value |
| No ICS treatment                                                                                                     | Ref  | -          | -       |
| Low-dose ICS                                                                                                         | 1.22 | 0.77; 1.93 | 0.392   |
| Moderate-dose ICS                                                                                                    | 1.24 | 0.72; 2.16 | 0.436   |
| High-dose ICS                                                                                                        | 3.81 | 2.51; 5.79 | <0.001  |
| CCI score 0-2                                                                                                        | Ref  | -          | -       |
| CCI score 3-4                                                                                                        | 0.83 | 0.50; 1.36 | 0.458   |
| CCI score +5                                                                                                         | 0.99 | 0.50; 1.96 | 0.970   |
| Female sex                                                                                                           | Ref  | -          | -       |
| Male sex                                                                                                             | 0.85 | 0.61; 1.20 | 0.349   |
| Year 2001-2004                                                                                                       | Ref  | -          | -       |
| Year 2005-2009                                                                                                       | 1.05 | 0.48; 2.34 | 0.896   |
| Year 2010-2014                                                                                                       | 2.08 | 1.03; 4.19 | 0.041   |
| Year 2015-2018                                                                                                       | 1.86 | 0.92; 3.74 | 0.084   |
| No OCS use                                                                                                           | Ref  | -          | -       |
| Low-dose OCS                                                                                                         | 0.77 | 0.46; 1.30 | 0.327   |
| High-dose OCS                                                                                                        | 1.17 | 0.72; 1.90 | 0.530   |
| Age, first quartile                                                                                                  | Ref  | -          | -       |
| Age, second quartile                                                                                                 | 0.88 | 0.52; 1.48 | 0.627   |
| Age, third quartile                                                                                                  | 1.51 | 0.88; 2.60 | 0.137   |
| Age, fourth quartile                                                                                                 | 1.48 | 0.77; 2.87 | 0.242   |

*Supplementary Table S4 - Results from cause-specific Cox proportional hazards regression with adjusted confounders. Low-dose ICS:  $\leq 400$   $\mu\text{g}$  budesonide equivalent/day. Moderate-dose ICS: 401-999  $\mu\text{g}$  budesonide equivalent/day. High-dose ICS:  $\geq 1,000$   $\mu\text{g}$  budesonide equivalent/day. Low-dose OCS  $\leq 750$  mg/year. High-dose OCS  $> 750$  mg/year. HR: Hazard ratio. CI: Confidence interval. ICS: Inhaled corticosteroids. CCI: Charlson Comorbidity Index. OCS: Oral corticosteroids.*

| <b>Supplementary Table S5 – Interaction analysis for sex</b> |        |       |
|--------------------------------------------------------------|--------|-------|
|                                                              | Female | Male  |
| No ICS treatment                                             | Ref.   | Ref.  |
| Low-dose ICS                                                 | Ref.   | 0.405 |
| Moderate-dose ICS                                            | Ref.   | 0.754 |
| High-dose ICS                                                | Ref.   | 0.046 |

*Supplementary Table S5 – P values for interaction analysis for sex. Low-dose ICS:  $\leq 400$   $\mu\text{g}$  budesonide equivalent/day. Moderate-dose ICS: 401-999  $\mu\text{g}$  budesonide equivalent/day. High-dose ICS:  $\geq 1,000$   $\mu\text{g}$  budesonide equivalent/day. ICS: Inhaled corticosteroid.*

| <b>Supplementary Table S6 – Interaction analysis for age</b> |                |                 |                |                 |
|--------------------------------------------------------------|----------------|-----------------|----------------|-----------------|
|                                                              | First quartile | Second quartile | Third quartile | Fourth quartile |
| No ICS treatment                                             | Ref.           | Ref.            | Ref.           | Ref.            |
| Low-dose ICS                                                 | Ref.           | 0.468           | 0.563          | 0.528           |
| Moderate-dose ICS                                            | Ref.           | 0.992           | 0.993          | 0.993           |
| High-dose ICS                                                | Ref.           | 0.971           | 0.619          | 0.459           |

*Supplementary Table 6 - P values for interaction analysis for age. Low-dose ICS:  $\leq 400$   $\mu\text{g}$  budesonide equivalent/day. Moderate-dose ICS: 401-999  $\mu\text{g}$  budesonide equivalent/day. High-dose ICS:  $\geq 1,000$   $\mu\text{g}$  budesonide equivalent/day. ICS: Inhaled corticosteroid.*

| <b>Supplementary Table S7 – Interaction analysis for concomitant COPD/asthma</b> |                |             |
|----------------------------------------------------------------------------------|----------------|-------------|
|                                                                                  | No COPD/asthma | COPD/asthma |
| No ICS treatment                                                                 | Ref.           | Ref.        |
| Low-dose ICS                                                                     | Ref.           | 0.886       |
| Moderate-dose ICS                                                                | Ref.           | 0.597       |
| High-dose ICS                                                                    | Ref.           | 0.715       |

*Supplementary Table S7 – P values for interaction analysis for concomitant COPD/asthma. Low-dose ICS:  $\leq 400$  µg budesonide equivalent/day. Moderate-dose ICS: 401-999 µg budesonide equivalent/day. High-dose ICS:  $\geq 1,000$  µg budesonide equivalent/day. ICS: Inhaled corticosteroid. COPD: Chronic obstructive pulmonary disease.*

| <b>Supplementary Table S8 – Interaction analysis for OCS treatment</b> |                  |                        |                         |
|------------------------------------------------------------------------|------------------|------------------------|-------------------------|
|                                                                        | No OCS treatment | Low-dose OCS treatment | High-dose OCS treatment |
| No ICS treatment                                                       | Ref.             | Ref.                   | Ref.                    |
| Low-dose ICS                                                           | Ref.             | 0.744                  | 0.311                   |
| Moderate-dose ICS                                                      | Ref.             | 0.835                  | 0.820                   |
| High-dose ICS                                                          | Ref.             | 0.919                  | 0.701                   |

*Supplementary Table S8 – P values for interaction analysis for OCS treatment. Low-dose ICS:  $\leq 400$   $\mu\text{g}$  budesonide equivalent/day. Moderate-dose ICS: 401-999  $\mu\text{g}$  budesonide equivalent/day. High-dose ICS:  $\geq 1,000$   $\mu\text{g}$  budesonide equivalent/day. Low-dose OCS  $\leq 750$  mg/year. High-dose OCS  $> 750$  mg/year. ICS: Inhaled corticosteroid. OCS: Oral corticosteroids.*

| <b>Supplementary Table S9 – Interaction analysis for antibiotic treatment</b> |                         |                    |
|-------------------------------------------------------------------------------|-------------------------|--------------------|
|                                                                               | No antibiotic treatment | Antibiotic treated |
| No ICS treatment                                                              | Ref.                    | Ref.               |
| Low-dose ICS                                                                  | Ref.                    | 0.071              |
| Moderate-dose ICS                                                             | Ref.                    | 0.538              |
| High-dose ICS                                                                 | Ref.                    | 0.837              |

*Supplementary Table S9 - P values for interaction analysis for antibiotic treatment. Low-dose ICS:  $\leq 400$   $\mu\text{g}$  budesonide equivalent/day. Moderate-dose ICS: 401-999  $\mu\text{g}$  budesonide equivalent/day. High-dose ICS:  $\geq 1,000$   $\mu\text{g}$  budesonide equivalent/day. ICS: Inhaled corticosteroid.*

| <b>Supplementary Table S10 – Results from Cox proportional hazards regression with ICS exposure as a time-varying covariate</b> |      |            |         |
|---------------------------------------------------------------------------------------------------------------------------------|------|------------|---------|
|                                                                                                                                 | HR   | 95% CI     | P value |
| No ICS treatment                                                                                                                | Ref. | Ref.       | Ref.    |
| Low-dose ICS                                                                                                                    | 0.53 | 0.30; 0.95 | 0.033   |
| Moderate-dose ICS                                                                                                               | 0.94 | 0.69; 1.29 | 0.717   |
| High dose-ICS                                                                                                                   | 1.89 | 1.44; 2.47 | <0.001  |

*Supplementary Table S10 - Results from Cox proportional hazards regression with ICS exposure as a time-varying covariate. Low-dose ICS: ≤400 µg budesonide equivalent/day. Moderate-dose ICS: 401-999 µg budesonide equivalent/day. High-dose ICS: ≥1,000 µg budesonide equivalent/day. ICS: Inhaled corticosteroids.*

| <b>Supplementary Table S11 – Results from IPTW analysis</b> |      |            |         |
|-------------------------------------------------------------|------|------------|---------|
|                                                             | HR   | 95% CI     | P value |
| No ICS treatment                                            | Ref. | Ref.       | Ref.    |
| Low-dose ICS                                                | 1.21 | 0.74; 1.98 | 0.439   |
| Moderate-dose ICS                                           | 1.16 | 0.65; 2.10 | 0.611   |
| High dose-ICS                                               | 3.69 | 2.42; 5.60 | <0.001  |

*Supplementary Table S11 - Results from IPTW Cox regression model. Low-dose ICS: ≤400 µg budesonide equivalent/day. Moderate-dose ICS: 401-999 µg budesonide equivalent/day. High-dose ICS: ≥1,000 µg budesonide equivalent/day. ICS: Inhaled corticosteroids.*

| <b>Supplementary Table S12 – Sensitivity analysis for 2<sup>nd</sup> <i>S. aureus</i> isolation</b> |      |            |         |
|-----------------------------------------------------------------------------------------------------|------|------------|---------|
|                                                                                                     | HR   | 95% CI     | P value |
| No ICS treatment                                                                                    | Ref  | Ref        | Ref     |
| Low-dose ICS                                                                                        | 1.47 | 0.65; 3.35 | 0.353   |
| Moderate-dose ICS                                                                                   | 1.70 | 0.49; 5.87 | 0.403   |
| High dose-ICS                                                                                       | 4.29 | 1.97; 9.33 | <0.001  |

Supplementary Table 12 - Sensitivity analysis for 2<sup>nd</sup> positive *S. aureus* culture adjusted for age (quartiles), sex (female vs. male), CCI score (0-2, 3-4, +5), total oral corticosteroid (OCS) use (no use, low-dose OCS (<median) and high-dose OCS (≥median) within 365 days prior to cohort entry and calendar year for entry into cohort (2001-2004, 2005-2009, 2010-2014, 2015-2018). Low-dose ICS: ≤400 µg budesonide equivalent/day. Moderate-dose ICS: 401-999 µg budesonide equivalent/day. High-dose ICS: ≥1,000 µg budesonide equivalent/day. ICS: Inhaled corticosteroids. HR: Hazard ratio. CI: Confidence interval. *S. aureus*: *Staphylococcus aureus*

| <b>Supplementary Table S13 – Sensitivity analysis for lower respiratory tract sampling sites</b> |      |            |         |
|--------------------------------------------------------------------------------------------------|------|------------|---------|
| <b>Sputum</b>                                                                                    |      |            |         |
|                                                                                                  | HR   | 95% CI     | P value |
| No ICS treatment                                                                                 | Ref  | Ref        | Ref     |
| Low-dose ICS                                                                                     | 1.20 | 0.69; 2.07 | 0.522   |
| Moderate-dose ICS                                                                                | 1.43 | 0.77; 2.65 | 0.258   |
| High dose-ICS                                                                                    | 4.84 | 3.03; 7.72 | <0.001  |
| <b>Other (tracheal secretion, bronchial secretion, bronchoalveolar lavage)</b>                   |      |            |         |
|                                                                                                  | HR   | 95% CI     | P value |
| No ICS treatment                                                                                 | Ref  | Ref        | Ref     |
| Low-dose ICS                                                                                     | 1.31 | 0.57; 2.99 | 0.526   |
| Moderate-dose ICS                                                                                | 0.83 | 0.24; 2.87 | 0.771   |
| High dose-ICS                                                                                    | 1.41 | 0.46; 4.38 | 0.550   |

*Supplementary Table S13 - Sensitivity analysis for lower respiratory tract sampling sites. Low-dose ICS: ≤400 µg budesonide equivalent/day. Moderate-dose ICS: 401-999 µg budesonide equivalent/day. High-dose ICS: ≥1,000 µg budesonide equivalent/day. ICS: Inhaled corticosteroids. HR: Hazard ratio. CI: Confidence interval. S. aureus: Staphylococcus aureus.*