**Supplementary materials - Understanding the burden of antibiotic resistance: a decade of carbapenem-resistant gram-negative bacterial infections in Italian intensive care units**

**Summary**

[**Coauthors:** 2](#_Toc161691392)

[**CLINICAL DEFINITION OF SPECIFIC INFECTIONS** 6](#_Toc161691394)

[**LOWER RESPIRATORY TRACT INFECTIONS** 6](#_Toc161691395)

[**BLOODSTREAM INFECTIONS (BSI)** 7](#_Toc161691396)

[**INTRA-ABDOMINAL INFECTIONS (IAI)** 8](#_Toc161691397)

[**URINARY TRACT INFECTIONS (UTIs)** 9](#_Toc161691398)

[**Supplementary Table 1**. 10](#_Toc161691399)

[**Supplementary Table 2.** 12](#_Toc161691401)

[**Supplementary Table 3** 13](#_Toc161691402)

[**Supplementary Table 4** 14](#_Toc161691403)

[**Supplementary Table 5** 15](#_Toc161691404)

[**Supplementary Figure 1** 16](#_Toc161691405)

[**Supplementary Figure 2** 17](#_Toc161691406)

[**Supplementary Figure 3** 20](#_Toc161691407)

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# **CLINICAL DEFINITION OF SPECIFIC INFECTIONS**

## **LOWER RESPIRATORY TRACT INFECTIONS**

* 1. **PNEUMONIA**:

Personalized from American Journal Infection Control 2008;36:309-332.

* POSSIBLE

Criterion 1: Presence of new and persistent infiltrate on chest x-ray/CT scan AND:

* Fever > 38° or leukocytes > 12,000/ml or < 4,000/ml
* Non quantitative culture from a sample of tracheal secretions
* At least two of the following:
  1. Purulent expectorate of new onset or alterations in characteristics of expectorate (colour, odour, quantity, consistency).
  2. Cough or dyspnea or tachypnea.
  3. Suggestive lung auscultation (rales or bronchial respiratory sounds), rhonchi or wheezing.
  4. Worsening of respiratory exchange (e.g. O2 desaturation or increase in request for O2 or increase in request for ventilation).

Criterion 2: Presence of new and persistent infiltrate on chest x-ray / CT scan AND:

* fever > 38°C or leukocytes > 12,000/ml or < 4,000/ml
* at least two of the following:
  1. purulent expectorate of new onset or alterations in characteristics of expectorate (colour, odour, quantity, consistency
  2. cough or dyspnea or tachypnea.
  3. suggestive lung auscultation (rales or bronchial respiratory sounds), rhonchi or wheezing.
  4. worsening of respiratory exchange (e.g. O2 desaturation or increase in request for O2 or increase in request for ventilation.
* PROBABLE / CERTAIN

Presence of new and persistent lung infiltrate AND at least 2 compatible clinical and laboratory signs:

* fever/hypothermia or leukocytosis/leukopenia
* purulent secretions of new onset and/or their modification or cough or dyspnea or tachypnea or suggestive auscultation or worsening of gas exchanges

AND 1 or more of the following criteria:

1. Positive culture, with quantitative assessment equal to/over threshold value of 105-6 CFU/ml, of one or more samples of secretions collected from the trachea by the unprotected method (tracheobronchial aspirate).
2. Positive culture, with quantitative assessment equal to/over the threshold value 103 CFU/ml for quantitative cultures collected by bronchial brush (Protected Specimen Brush PSB) or ≥ 104 CFU/ml for quantitative cultures collected by bronchoalveolar lavage (BAL) or mini-BAL or ≥ 103 protected distal aspiration. PN 1
3. Concordant blood culture with organisms isolated from respiratory tract secretions. PN 3
4. Positive culture of a pleural effusion with organism concordant with organisms isolated from respiratory tract secretions.
5. Evolution and abscessualization of lung focus.
6. Other certain infectious data on viruses or particular germs (e.g. Legionella from respiratory secretions, positivity of urinary antigen for *Legionella*, *Pneumococcus*, isolation of mycobacteria, detection of *P. jirovecii*, isolation of *Aspergillus* hyphae, serum conversion with significant increase in antibody titre, presence of antigens and/or viral antibodies detected in respiratory secretions, other).
   1. **VENTILATOR ASSOCIATED PNEUMONIA (VAP)** (<https://www.cdc.gov/nhsn/pdfs/pscmanual/6pscvapcurrent.pdf>)

A pneumonia where the patient is on mechanical ventilation for > 2 consecutive calendar days on the date of event, with day of ventilator placement being Day 1\* AND the ventilator was in place on the date of event or the day before.

\*If the ventilator was in place prior to inpatient admission, the ventilator day count begins with the admission date to the first inpatient location. If a break in mechanical ventilation occurs for at least one full calendar day, ventilator day count for ventilator association starts anew upon reintubation and/or re-initiation of mechanical ventilation.

## **BLOODSTREAM INFECTIONS (BSI)**

(CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting, Doi: [10.1016/j.ajic.2008.03.002](https://doi.org/10.1016/j.ajic.2008.03.002))

* 1. **Primary bacteraemia of unknown origin:**

A Laboratory Confirmed Bloodstream Infection (LCBI) that is not secondary to an infection at another body site.

* Absence of a recognized focus of infection

OR

* Organism is not related to an infection at another site

Definition of laboratory-confirmed bloodstream infection (LCBI), at least 1 of the following criteria:

1. Recognized pathogen cultured from 1 or more blood cultures AND organism cultured from blood is not related to an infection at another site. (See Notes 1 and 2)
2. Patient has at least 1 of the following signs or symptoms: fever (> 38°C), chills, or hypotension and signs and symptoms AND positive laboratory results are not related to an infection at another site AND common skin contaminant (i.e., diphtheroids [*Corynebacterium* spp], *Bacillus* [not *B. anthracis*] spp, *Propionibacterium* spp, coagulase-negative *Staphylococci* [including *S. epidermidis*], viridians group *Streptococci*, *Aerococcus* spp, *Micrococcus* spp) is cultured from 2 or more blood cultures drawn on separate occasions. (See Notes 3 and 4).

Notes

1. In criterion 1, the phrase “1 or more blood cultures” means that at least 1 bottle from a blood draw is reported by the laboratory as having grown organisms (i.e., is a positive blood culture).

2. In criterion 1, the term “recognized pathogen” does not include organisms considered common skin contaminants (see criteria 2 and 3 for a list of common skin contaminants). A few of the recognized pathogens are *S. aureus*, *Enterococcus* spp, *E. coli*, *Pseudomonas* spp, *Klebsiella* spp, *Candida* spp, and others.

3. In criteria 2 and 3, the phrase “2 or more blood cultures drawn on separate occasions” means (1) that blood from at least 2 blood draws were collected within 2 days of each and (2) that at least 1 bottle from each blood draw is reported by the laboratory as having grown the same common skin contaminant organism.

* 1. **Intravascular catheter-related BSI (CR-BSI):**

(Guidelines for the Prevention of Intravascular Catheter-related Infections, doi: [10.1093/cid/cir257](https://doi.org/10.1093%2Fcid%2Fcir257))

Presence of clinical suspicion (signs of systemic inflammation as fever, hypotension, chills) AND no other apparent source of bacteraemia/fungaemia with the exception of the catheter AND one of the following criteria:

1. semiquantitative (> 15 CFU) or quantitative culture (>103 CFU) of a catheter segment with a concordant (species and antibiogram) blood culture (not necessarily quantitative) performed at the same time (within 24 hours) as catheter removal
2. differential time to positivization (at least 120 minutes) for qualitative blood culture from blood drawn through the catheter and blood culture from a peripheral vein.
3. same time to positivization of quantitative blood cultures, but with ratio of ≥ 5:1 between blood culture from vascular catheter vs blood culture from peripheral vein
   1. **Secondary BSI:**

A BSI secondary to another site of infection with the following criteria:

* An NHSN site-specific definition must be met:
* One of the following scenarios must be met:
* At least one organism from the blood specimen matches an organism identified from the site specific specimen that is used as an element to meet the NHSN site-specific infection criterion AND the blood specimen is collected during the secondary BSI attribution period (infection window period + repeat infection timeframe)
* An organism identified in the blood specimen is an element that is used to meet a NHSN site specific infection criterion, and therefore is collected during the site-specific infection window period.

## **INTRA-ABDOMINAL INFECTIONS (IAI)**

Personalized from Critical Care Medicine 2003;31:2228-2237

* 1. **Primary peritonitis:**

Peritoneal infection in the absence of visceral lesions, as infected ascites, infections in peritoneal dialysis etc.

* 1. **Secondary peritonitis:**

Localized or diffuse peritoneal infection due to a solution of continuity in gastroenteric tract, as appendicular abscess, perforation of the viscera, pancreatitis, retroperitoneal infection, etc..

* 1. **Tertiary peritonitis:**

Primary or secondary peritonitis which, despite treatment, recurs as a more severe infection with development of multiorgan failure: this occurs in weak and frail patients and is the result both of failure to control the initial focus and of the lowering of patient defences.

* 1. **Post-surgical peritonitis:**

Peritonitis or abscess or pancreatitis or retroperitoneal infections such as complications of previous surgical procedures.

* 1. **Infected acute pancreatitis:**

Acute pancreatitis + positive blood culture (in the absence of other sites of infection and/or CT-scan documentation of retroperitoneal air bubbles and/or positive culture of pancreatic tissue or drainage material or material withdrawn during surgery.

## **URINARY TRACT INFECTIONS (UTIs)**

(Personalized from American Journal Infection Control 2008;36:309-332)

* Positive urinoculture load > 105 or load between 103 and 105 in the presence of antibiotic therapy with no more than 2 species of organism.

AND

* Clinical signs compatible with UTI (fever >38°C in the absence of other causes, pyuria, cloudy urine)
* Leukocyturia (when using stick test: at least 2nd step) : ≥ 10 leukocytes/cc

**Supplementary Table 1**. Study cohort characteristics and intensive care unit outcomes

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Number of patients** | **Total** | **2013** | **2014** | **2015** | **2016** | **2017** | **2018** | **2019** | **2020** | **2021** | **2022** |
| 299280 | 29068 | 28267 | 27585 | 33164 | 33794 | 32885 | 36897 | 25569 | 27018 | 25033 |
| **Male Sex (%)** | 180477 (60.3%) | 17252 (59.4%) | 16754 (59.3%) | 16495 (59.8%) | 19806 (59.7%) | 20050 (59.3%) | 19609 (59.6%) | 22241 (60.3%) | 15936 (62.3%) | 16920 (62.6%) | 15414 (61.6%) |
| **Age > 65 (%)** | 181382 (60.6%) | 17941 (61.7%) | 17220 (60.9%) | 17137 (62.1%) | 20481 (61.8%) | 20961 (62.0%) | 20053 (61.0%) | 22268 (60.4%) | 15094 (59.0%) | 15490 (57.3%) | 14737 (58.9%) |
| **ICU LOS (Mean ± SD)** | 6 ± 10 | 6 ± 10 | 6 ± 10 | 6 ± 10 | 6 ± 10 | 6 ± 9 | 6 ± 10 | 6 ± 9 | 8 ± 11 | 8 ± 12 | 7 ± 11 |
| **Trauma** | 40033 (13.4%) | 4178 (14.4%) | 4093 (14.5%) | 3869 (14.1%) | 4457 (13.5%) | 4464 (13.2%) | 4406 (13.4%) | 4983 (13.5%) | 2938 (11.5%) | 3293 (12.2%) | 3352 (13.4%) |
| **ICU-outcomes** | | | | | | | | | | | |
| **Death** | 52345 (17.5%) | 4948 (17.0%) | 4816 (17.1%) | 4755 (17.3%) | 5541 (16.7%) | 5766 (17.1%) | 5460 (16.7%) | 5960 (16.2%) | 5160 (20.3%) | 5510 (20.5%) | 4429 (17.8%) |
| **Transferred within same hospital** | 216139 (72.4%) | 21224 (73.1%) | 20644 (73.1%) | 19992 (72.8%) | 24349 (73.5%) | 24847 (73.6%) | 24053 (73.4%) | 27198 (74.0%) | 17417 (68.5%) | 18583 (69.0%) | 17832 (71.6%) |
| **Transferred to other hospital** | 26783 (9.0%) | 2553 (8.8%) | 2449 (8.7%) | 2416 (8.8%) | 2878 (8.7%) | 2808 (8.3%) | 2926 (8.9%) | 3260 (8.9%) | 2599 (10.2%) | 2560 (9.5%) | 2334 (9.4%) |
| **Discharged home** | 1981 (0.7%) | 232 (0.8%) | 196 (0.7%) | 180 (0.7%) | 225 (0.7%) | 195 (0.6%) | 200 (0.6%) | 211 (0.6%) | 148 (0.6%) | 177 (0.7%) | 217 (0.9%) |
| **Palliative care** | 1132 (0.4%) | 79 (0.3%) | 124 (0.4%) | 112 (0.4%) | 113 (0.3%) | 123 (0.4%) | 123 (0.4%) | 146 (0.4%) | 113 (0.4%) | 106 (0.4%) | 93 (0.4%) |
| **Previous ward** |  | | | | | | | | | | |
| **Medical** | 45817 (15.4%) | 4178 (14.4%) | 4060 (14.4%) | 3936 (14.4%) | 4733 (14.4%) | 4786 (14.3%) | 4671 (14.3%) | 5117 (14.0%) | 5097 (20.1%) | 5453 (20.3%) | 3786 (15.2%) |
| **Surgical** | 122674 (41.3%) | 13187 (45.6%) | 12337 (43.9%) | 11639 (42.5%) | 14136 (42.9%) | 14590 (43.5%) | 13682 (41.9%) | 15829 (43.2%) | 8586 (33.8%) | 9080 (33.8%) | 9608 (38.6%) |
| **Emergency** | 101383 (34.1%) | 9233 (31.9%) | 9305 (33.1%) | 9285 (33.9%) | 11308 (34.3%) | 11295 (33.6%) | 11315 (34.7%) | 12534 (34.2%) | 8737 (34.4%) | 9134 (34.0%) | 9237 (37.2%) |
| **Other ICU** | 18624 (6.3%) | 1578 (5.5%) | 1739 (6.2%) | 1735 (6.3%) | 1860 (5.6%) | 1988 (5.9%) | 2112 (6.5%) | 2228 (6.1%) | 1973 (7.8%) | 1848 (6.9%) | 1563 (6.3%) |
| **High dependency unit** | 8873 (3.0%) | 751 (2.6%) | 676 (2.4%) | 785 (2.9%) | 923 (2.8%) | 917 (2.7%) | 854 (2.6%) | 938 (2.6%) | 987 (3.9%) | 1376 (5.1%) | 666 (2.7%) |

ICU: intensive care unit; LOS: length of stay; SD: standard deviation

**Supplementary Table 2.** Details on hospital-acquired infections diagnosed in intensive care unit during the study period

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Total** | **2013** | **2014** | **2015** | **2016** | **2017** | **2018** | **2019** | **2020** | **2021** | **2022** |
| **Patients with ICU-HAIs** | 20570 | 1818 | 1865 | 1676 | 1865 | 1979 | 1856 | 2050 | 1319 | 1600 | 1650 |
| **HAIs** | 25964 | 2471 | 2412 | 2303 | 2470 | 2693 | 2682 | 2239 | 2889 | 3527 | 2280 |
| **Mean ICU-HAI per patient** | 1.5 | 1.36 | 1.29 | 1.37 | 1.32 | 1.36 | 1.45 | 1.09 | 2.19 | 2.21 | 1.38 |
| **GNB infections**  **(% on ICU-HAIs)** | 12060 (46.5%) | 1236 | 1199 | 1187 | 1200 | 1264 | 1304 | 969 | 1282 | 1461 | 958 |
| **CR-GNB infections**  **(% on ICU-HAIs)** | 2927 (11.3%) | 337 | 303 | 321 | 320 | 305 | 262 | 222 | 312 | 328 | 217 |
| **PA infections**  **(% on ICU-HAIs)** | 4818  (18.6%) | 439 (17.77%) | 448 (18.57%) | 461 (20.02%) | 445 (18.02%) | 547 (20.31%) | 540 (20.13%) | 413 (18.45%) | 513 (17.8%) | 593 (16.8%) | 419 (18.4%) |
| **CRPA infections**  **(% on PA infections)** | 1049  (21.8%) | 114  (26 %) | 90  (20.1 %) | 109  (23.6 %) | 110  (24.7 %) | 109  (19.9 %) | 84  (15.6 %) | 81  (19.6 %) | 106 (20.7 %) | 140 (23.6 %) | 106 (25.3 %) |
| ***Acinetobacter* spp. infections**  **(% on ICU-HAIs)** | 2183  (8.4%) | 303 (12.26%) | 265 (10.99%) | 232 (10.07%) | 243 (9.84%) | 214 (7.95%) | 202 (7.53%) | 124 (5.54%) | 236 (8.2%) | 244 (6.9%) | 120 (5.3%) |
| **CR-*Acinetobacter* spp infections**  **(% on *Acinetobacter* spp infections)** | 290  (13.3%) | 41 (13.5%) | 26 (9.8%) | 26 (11.2%) | 22 (9.1%) | 33 (15.4%) | 39 (19.3%) | 26 (21%) | 19 (8.1%) | 35 (14.3%) | 23 (19.2%) |
| ***Klebsiella* spp. infections**  **(% on ICU-HAIs)** | 5059  (19.5%) | 494 (19.99%) | 486 (20.15%) | 494 (21.45%) | 512 (20.73 %) | 503 (18.68 %) | 562 (20.95 %) | 432 (19.29 %) | 533 (18.4%) | 624 (17.7%) | 419 (18.4%) |
| **CR-Klebsiella spp. infections**  **(% on *Klebsiella* spp infections)** | 1588  (31.4%) | 182 (36.8 %) | 187 (38.5 %) | 186 (37.7 %) | 188  (36.7 %) | 163  (32.4 %) | 139  (24.7 %) | 115  (26.6 %) | 187 (35.1 %) | 153 (24.5 %) | 88  (21 %) |

ICU: intensive care unit; HAI: hospital-acquired infection; GNB: gram-negative bacteria; CR: carbapenem-resistant; CR-GNB: carbapenem-resistant gram-negative bacteria; PA: *Pseudomonas aeruginosa*; CRPA: carbapenem-resistant *Pseudomonas aeruginosa*

**Supplementary Table 3.** Details on infections by *Pseudomonas aeruginosa* acquired in intensive care unit during the study period

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **2013** | **2014** | **2015** | **2016** | **2017** | **2018** | **2019** | **2020** | **2021** | **2022** |
| **Total VAP episodes** | 856 | 756 | 699 | 798 | 763 | 827 | 714 | 1237 | 1664 | 946 |
| **VAP by PA**  **(% on VAP episodes)** | 183  (21.38 %) | 170  (22.49 %) | 155  (22.17 %) | 188  (23.56 %) | 187  (24.51 %) | 207  (25.03 %) | 174  (24.37 %) | 250 (20.2%) | 333  (20%) | 208  (22%) |
| **VAP by CRPA**  **(% on VAP by PA)** | 60  (32.8 %) | 32  (18.8 %) | 45  (29 %) | 43  (22.9 %) | 41  (21.9 %) | 35  (16.9 %) | 35  (20.1 %) | 56  (22.4 %) | 82  (24.6 %) | 58  (27.9 %) |
| **Total BSI episodes** | 283 | 257 | 256 | 258 | 308 | 315 | 285 | 348 | 392 | 238 |
| **BSI by PA**  **(% on BSI episodes)** | 20  (7.07 %) | 21  (8.17 %) | 22  (8.59 %) | 20  (7.75 %) | 27  (8.77 %) | 30  (9.52 %) | 24  (8.42 %) | 25  (7.2%) | 24  (6.1%) | 10  (4.2%) |
| **BSI by CRPA**  **(% on BSI by PA)** | 3  (15 %) | 7  (33.3 %) | 4  (18.2 %) | 9  (45 %) | 4  (14.8 %) | 4  (13.3 %) | 2  (8.3 %) | 6  (24 %) | 7  (29.2 %) | 3  (30 %) |
| **Total UTI episodes** | 106 | 94 | 83 | 89 | 86 | 71 | 67 | 431 | 567 | 365 |
| **UTI by PA**  **(% on UTI episodes)** | 12  (11.32 %) | 12  (12.77 %) | 8  (9.64 %) | 8  (8.99 %) | 16  (18.6 %) | 11  (15.49 %) | 10  (14.93 %) | 65 (15.1%) | 74 (13.1%) | 53 (14.5%) |
| **UTI by CRPA** | 3  (25 %) | 2  (16.7 %) | 4  (50 %) | 0  (0 %) | 1  (6.2 %) | 1  (9.1 %) | 1  (10 %) | 12  (18.5 %) | 13  (17.6 %) | 10  (18.9 %) |
| **Total IAI episodes** | 219 | 196 | 216 | 199 | 230 | 250 | 186 | 84 | 164 | 177 |
| **IAI by PA**  **(% on IAI episodes)** | 33  (15.07 %) | 36  (18.37 %) | 33  (15.28 %) | 38  (19.1 %) | 47  (20.43 %) | 50  (20 %) | 40  (21.51 %) | 19  (22.6%) | 28  (17.1%) | 37  (20.9%) |
| **IAI by CRPA**  **(% on IAI by PA)** | 12  (36.4 %) | 7  (19.4 %) | 11  (33.3 %) | 16  (42.1 %) | 15  (31.9 %) | 12  (24 %) | 13  (32.5 %) | 4  (21.1 %) | 8  (28.6 %) | 11  (29.7 %) |

VAP: ventilator associated-pneumonia; PA: *Pseudomonas aeruginosa;* CRPA: carbapenem-resistant *Pseudomonas aeruginosa;* BSI: bloodstream infection; UTI: urinary tract infection; IAI: intrabdominal infection

**Supplementary Table 4.** Details on infections by *Klebsiella* spp. acquired in intensive care unit during the study period

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **2013** | **2014** | **2015** | **2016** | **2017** | **2018** | **2019** | **2020** | **2021** | **2022** |
| **Total VAP episodes** | 856 | 756 | 699 | 798 | 763 | 827 | 714 | 1237 | 1664 | 946 |
| **VAP by *Klebsiella* spp.**  **(% on VAP episodes)** | 211  (24.65 %) | 179  (23.68 %) | 188  (26.9 %) | 210  (26.32 %) | 160  (20.97 %) | 227  (27.45 %) | 182  (25.49 %) | 250 (20.2%) | 348 (20.9%) | 194 (20.5%) |
| **VAP by CR-*Klebsiella***  **(% on VAP by *Klebsiella*)** | 74  (35.1 %) | 72  (40.2 %) | 75  (39.9 %) | 72  (34.3 %) | 52  (32.5 %) | 57  (25.1 %) | 49  (26.9 %) | 101  (40.4 %) | 89  (25.6 %) | 46  (23.7 %) |
| **Total BSI episodes** | 283 | 257 | 256 | 258 | 308 | 315 | 285 | 348 | 392 | 238 |
| **BSI by *Klebsiella* spp.**  **(% on BSI episodes)** | 34  (12.01 %) | 40  (15.56 %) | 44  (17.19 %) | 52  (20.16 %) | 52  (16.88 %) | 46  (14.6 %) | 50  (17.54 %) | 63 (18.1%) | 54 (13.8%) | 32 (13.4%) |
| **BSI by CR-*Klebsiella***  **(% on BSI by *Klebsiella*)** | 10  (29.4 %) | 19  (47.5 %) | 12  (27.3 %) | 22  (42.3 %) | 22  (42.3 %) | 13  (28.3 %) | 17  (34 %) | 27  (42.9 %) | 13  (24.1 %) | 6  (18.8 %) |
| **Total UTI episodes** | 106 | 94 | 83 | 89 | 86 | 71 | 67 | 431 | 567 | 365 |
| **UTI by *Klebsiella* spp.**  **(% on UTI episodes)** | 23  (21.7 %) | 10  (10.64 %) | 22  (26.51 %) | 15  (16.85 %) | 21  (24.42 %) | 16  (22.54 %) | 10  (14.93 %) | 58  (13.5%) | 71  (12.5%) | 51  (14%) |
| **UTI by CR-*Klebsiella*** | 13  (56.5 %) | 3  (30 %) | 13  (59.1 %) | 6  (40 %) | 10  (47.6 %) | 5  (31.2 %) | 4  (40 %) | 17  (29.3 %) | 24  (33.8 %) | 14  (27.5 %) |
| **Total IAI episodes** | 219 | 196 | 216 | 199 | 230 | 250 | 186 | 84 | 164 | 177 |
| **IAI by *Klebsiella***  **(% on IAI episodes)** | 44  (20.09 %) | 44  (22.45 %) | 51  (23.61 %) | 47  (23.62 %) | 42  (18.26 %) | 50  (20 %) | 30  (16.13 %) | 19  (22.6%) | 29  (17.7%) | 32  (18.1%) |
| **IAI by CR-*Klebsiella***  **(% on IAI by *Klebsiella*)** | 28  (63.6 %) | 23  (52.3 %) | 21  (41.2 %) | 25  (53.2 %) | 18  (42.9 %) | 22  (44 %) | 11  (36.7 %) | 6  (31.6 %) | 14  (48.3 %) | 12  (37.5 %) |

VAP: ventilator associated-pneumonia; CR: carbapenem-resistant*;* BSI: bloodstream infection; UTI: urinary tract infection; IAI: intrabdominal infection

**Supplementary Table 5.** Details on infections by *Acinetobacter* spp. acquired in intensive care unit during the study period

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **2013** | **2014** | **2015** | **2016** | **2017** | **2018** | **2019** | **2020** | **2021** | **2022** |
| **Total VAP episodes** | 856 | 756 | 699 | 798 | 763 | 827 | 714 | 1237 | 1664 | 946 |
| **VAP by *Acinetobacter* spp.**  **(% on VAP episodes)** | 167 (19.51 %) | 120 (15.87 %) | 113 (16.17 %) | 132 (16.54 %) | 104 (13.63 %) | 98  (11.85 %) | 59  (8.26 %) | 171  (13.8%) | 130  (7.8%) | 52 (5.5%) |
| **VAP by CR-** ***Acinetobacter***  **(% on VAP by *Klebsiella*)** | 21  (12.6 %) | 12  (10 %) | 10  (8.8 %) | 8  (6.1 %) | 14  (13.5 %) | 17  (17.3 %) | 9  (15.3 %) | 11  (6.4 %) | 17  (13.1 %) | 11  (21.2 %) |
| **Total BSI episodes** | 283 | 257 | 256 | 258 | 308 | 315 | 285 | 348 | 392 | 238 |
| **BSI by *Acinetobacter* spp.**  **(% on BSI episodes)** | 14  (4.95 %) | 14  (5.45 %) | 12  (4.69 %) | 11  (4.26 %) | 14  (4.55 %) | 12  (3.81 %) | 15  (5.26 %) | 16  (4.6%) | 27  (6.9%) | 12  (5%) |
| **BSI by CR-** ***Acinetobacter***  **(% on BSI by *Acinetobacter*)** | 2  (14.3 %) | 0  (0 %) | 0  (0 %) | 1  (9.1 %) | 3  (21.4 %) | 3  (25 %) | 3  (20 %) | 0  (0 %) | 5  (18.5 %) | 2  (16.7 %) |
| **Total UTI episodes** | 106 | 94 | 83 | 89 | 86 | 71 | 67 | 431 | 567 | 365 |
| **UTI by *Acinetobacter* spp.**  **(% on UTI episodes)** | 16  (15.09 %) | 8  (8.51 %) | 7  (8.43 %) | 7  (7.87 %) | 5  (5.81 %) | 2  (2.82 %) | 2  (2.99 %) | 10  (2.3%) | 13  (2.3%) | 7  (1.9%) |
| **UTI by CR-** ***Acinetobacter*** | 3  (18.8 %) | 0  (0 %) | 0  (0 %) | 0  (0 %) | 0  (0 %) | 0  (0 %) | 0  (0 %) | 2  (20 %) | 2  (15.4 %) | 0  (0 %) |
| **Total IAI episodes** | 219 | 196 | 216 | 199 | 230 | 250 | 186 | 84 | 164 | 177 |
| **IAI by *Acinetobacter***  **(% on IAI episodes)** | 35  (15.98 %) | 23  (11.73 %) | 20  (9.26 %) | 17  (8.54 %) | 14  (6.09 %) | 21  (8.4 %) | 11  (5.91 %) | 7  (8.3%) | 11  (6.7%) | 12  (6.8%) |
| **IAI by CR-** ***Acinetobacter***  **(% on IAI by *Acinetobacter*)** | 1  (2.9 %) | 2  (8.7 %) | 4  (20 %) | 1  (5.9 %) | 1  (7.1 %) | 4  (19 %) | 0  (0 %) | 0  (0 %) | 1  (9.1 %) | 0  (0 %) |

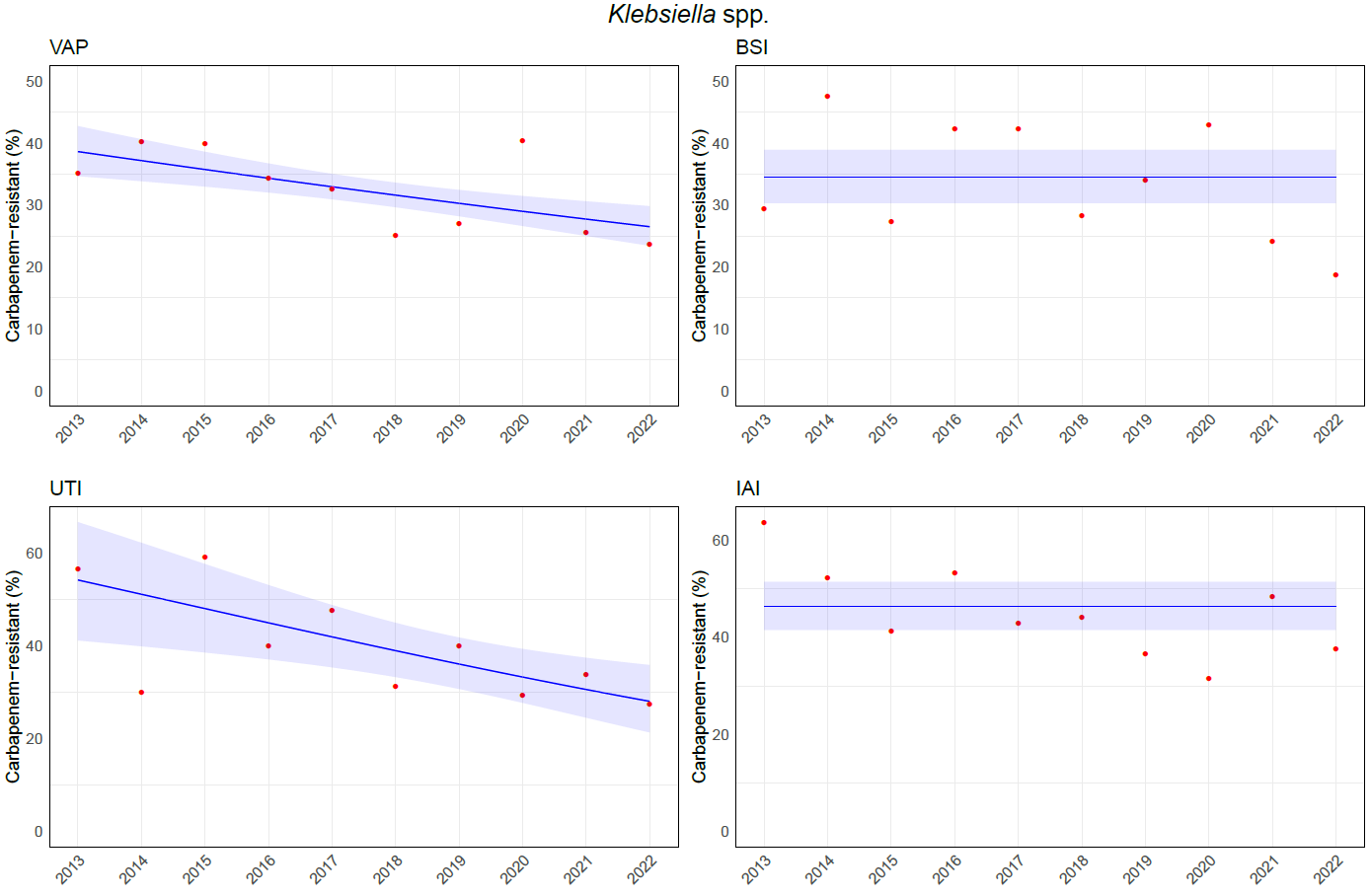
VAP: ventilator associated-pneumonia; CR: carbapenem-resistant*;* BSI: bloodstream infection; UTI: urinary tract infection; IAI: intrabdominal infection

**Supplementary Figure 1.** *Pseudomonas aeruginosa* carbapenem-resistance trend over years in different infection site

A screenshot of a graph

Description automatically generated

**Supplementary Figure 2.** *Klebsiella* spp. carbapenem-resistance trend over years in different infection site



**Supplementary Figure 3.** *Acinetobacter* spp. carbapenem-resistance trend over years in different infection site  
A screenshot of a graph

Description automatically generated

**Supplemental models result.**

**a) Percentage of infections.**

For VAPs we selected the 5th grade orthogonal polynomial:

|  |  |  |  |
| --- | --- | --- | --- |
|  | Estimate | Std. Error | Wald test p-value |
| Intercept | –0.622 | 0.013 | < 0.001 |
| 1st degree polynomial | 0.554 | 0.041 | < 0.001 |
| 2nd degree polynomial | 0.419 | 0.042 | < 0.001 |
| 3rd degree polynomial | –0.189 | 0.042 | < 0.001 |
| 4th degree polynomial | –0.272 | 0.041 | < 0.001 |
| 5th degree polynomial | –0.222 | 0.041 | < 0.001 |

which corresponds to:

η = – 0.852 + 0.083\*year + 0.083\*year2 + 0.011\*year3 – 0.004 \*year4 – 0.0008\*year5

where η is the linear predictor and the variable *year* represents the year shifted by the weighted mean of the observations. We will use this notation throughout all the **Supplemental models result**.

The p–value of the log–likelihood ratio test with respect to the null model is: p <0.001.

For BSI there was no significant trend (p–value = 0.615), and the model is:

|  |  |  |  |
| --- | --- | --- | --- |
|  | Estimate | Std. Error | Wald test p-value |
| Intercept | –2.058 | 0.019 | < 0.001 |

which corresponds to:

η = – 2.058

For UTI the 4th grade polynomial was chosen through a forward selection (p-value < 0.001):

|  |  |  |  |
| --- | --- | --- | --- |
|  | Estimate | Std. Error | Wald test p-value |
| Intercept | –2.808 | 0.030 | < 0.001 |
| 1st degree polynomial | 1.788 | 0.082 | < 0.001 |
| 2nd degree polynomial | 1.211 | 0.093 | < 0.001 |
| 3rd degree polynomial | –0.305 | 0.089 | < 0.001 |
| 4th degree polynomial | –0.77842 | 0.081 | < 0.001 |

which corresponds to the model for the linear predictor:

η = –3.354 + 0.447\*year + 0.160\*year2 – 0.018\*year3 – 0.006\*year4

The percentage of IAI showed a linear trend (p–value < 0.001) where the coefficients of the model are:

|  |  |  |  |
| --- | --- | --- | --- |
|  | Estimate | Std. Error | Wald test p-value |
| Intercept | –2.563 | 0.024 | < 0.001 |
| 1st degree polynomial | –0.065 | 0.008 | < 0.001 |

which corresponds to:

η = –2.563 – 0.065\*year

**b) VAP and CR–BSI incidence rate**

For VAP incidence rate a 5th grade polynomial was selected (p–value < 0.001). The coefficients of the model are:

|  |  |  |  |
| --- | --- | --- | --- |
|  | Estimate | Std. Error | Wald test p-value |
| Intercept | – 4.621 | 0.021 | < 0.001 |
| 1st degree polynomial | 0.531 | 0.018 | < 0.01 |
| 2nd degree polynomial | 0.388 | 0.005 | < 0.001 |
| 3rd degree polynomial | – 0.122 | 0.003 | < 0.001 |
| 4th degree polynomial | – 0.150 | 0.0002 | < 0.001 |
| 5th degree polynomial | – 0.09 | 0.0001 | < 0.01 |

that corresponds to:

η = – 4.812 + 0.054\*year + 0.042\*year2 + 0.006\*year3 – 0.001\*year4 – 0.0003\*year5

For CR–BSI we stopped at the 4th degree (p–value < 0.001) and the model coefficients are:

|  |  |  |  |
| --- | --- | --- | --- |
|  | Estimate | Std. Error | Wald test p-value |
| Intercept | – 6.061 | 0.033 | < 0.001 |
| 1st degree polynomial | 0.447 | 0.015 | < 0.001 |
| 2nd degree polynomial | 0.074 | 0.009 | 0.180 |
| 3rd degree polynomial | – 0.192 | 0.0009 | < 0.001 |
| 4th degree polynomial | – 0.237 | 0.0004 | < 0.001 |

that corresponds to:

η = – 6.1659191 + 0.108\*year + 0.040\*year2 – 0.004\*year3 – 0.002\*year4

**c) Multi–drug resistance microorganism**

A U–shaped correlation was found for *Pseudomonas aeruginosa* (p–value < 0.01). The coefficients of the model are:

|  |  |  |  |
| --- | --- | --- | --- |
|  | Estimate | Std. Error | Wald test p-value |
| Intercept | –1.278 | 0.035 | < 0.001 |
| 1st degree polynomial | –0.046 | 0.109 | 0.67 |
| 2nd degree polynomial | 0.397 | 0.111 | < 0.001 |

which is represented by:

η = –1.419 – 0.012\*year + 0.017\*year2

For *Klebsiella* spp. a linear trend was found (p-value < 0.001), where the coefficients of the model are:

|  |  |  |  |
| --- | --- | --- | --- |
|  | Estimate | Std. Error | Wald test p-value |
| Intercept | –0.789 | 0.030 | <0.001 |
| 1st degree polynomial | –0.736 | 0.098 | <0.001 |

that corresponds to:

η = – 0.830 – 0.081\*year

*Acinetobacter* spp. did not show any trend (p-value = 0.065). The corresponding null model is:

|  |  |  |  |
| --- | --- | --- | --- |
|  | Estimate | Std. Error | Wald test p-value |
| Intercept | 1.876 | 0.063 | <0.001 |

that is:

η = 1.876

**d) Carbapenem–resistant microorganisms**

***Pseudomonas aeruginosa***

We analysed the presence of carbapenem–resistant *Pseudomonas aeruginosa* according to the different infection site. The only infections where a trend for MDR was found are VAPs, which have a U–shaped relation for the linear predictor (p–value < 0.01) and the model coefficients are:

|  |  |  |  |
| --- | --- | --- | --- |
|  | Estimate | Std. Error | Wald test p-value |
| Intercept | –1.177 | 0.053 | < 0.001 |
| 1st degree polynomial | –0.135 | 0.157 | 0.391 |
| 2nd degree polynomial | 0.559 | 0.165 | < 0.001 |

corresponding to the following relation:

η = –1.38 – 0.009\*year + 0.024\*year2

For BSI there is no trend (p-value = 0.941) and the estimate is:

|  |  |  |  |
| --- | --- | --- | --- |
|  | Estimate | Std. Error | Wald test p-value |
| Intercept | –1.267 | 0.162 | <0.001 |

that corresponds to:

η = –1.267

Also for UTI there is no trend (p-value = 0.821), and the estimate is:

|  |  |  |  |
| --- | --- | --- | --- |
|  | Estimate | Std. Error | Wald test p-value |
| Intercept | –1.552 | 0.161 | <0.001 |

that corresponds to:

η = –1.552

There is no trend for IAI either (p-value = 0.905) with coefficient:

|  |  |  |  |
| --- | --- | --- | --- |
|  | Estimate | Std. Error | Wald test p-value |
| Intercept | –0.838 | 0.115 | <0.001 |

that corresponds to:

η = –0.838

***Klebsiella* spp.**

*Klebsiella* spp. showed a tendency to decrease with a linear trend in VAP (p–value < 0.001). The coefficients of the models are:

|  |  |  |  |
| --- | --- | --- | --- |
|  | Estimate | Std. Error | Wald test p-value |
| Intercept | –0.742 | 0.046 | <0.001 |
| 1st degree polynomial | –0.562 | 0.145 | <0.001 |

which corresponds to:

η = – 0.773 – 0.062\*year

We notice a decreasing trend also for UTI (p–value < 0.01), which model reads:

|  |  |  |  |
| --- | --- | --- | --- |
|  | Estimate | Std. Error | Wald test p-value |
| Intercept | –0.385 | 0.132 | <0.01 |
| 1st degree polynomial | –1.119 | 0.379 | <0.01 |

which corresponds to:

η = – 0.447 – 0.123\*year

For BSI (p-value = 0.133) there was no trend, where respectively:

|  |  |  |  |
| --- | --- | --- | --- |
|  | Estimate | Std. Error | Wald test p-value |
| Intercept | –0.642 | 0.097 | <0.001 |

i.e.

η = – 0.642

There is no trend for IAI either (p-value = 0.905), with coefficient:

|  |  |  |  |
| --- | --- | --- | --- |
|  | Estimate | Std. Error | Wald test p-value |
| Intercept | –0.145 | 0.102 | 0.156 |

i.e.

η = – 0.145

***Acinetobacter* spp.**

For *Acinetobacter* spp. there was no trend that correlate the presence of carbapenem–resistant strains with time. In particular:

For VAP (p-value = 0.350), the coefficient is:

|  |  |  |  |
| --- | --- | --- | --- |
|  | Estimate | Std. Error | Wald test p-value |
| Intercept | 2.056 | 0.093 | <0.001 |

that is:

η = 2.056

For BSI (p-value = 0.237), the coefficient is:

|  |  |  |  |
| --- | --- | --- | --- |
|  | Estimate | Std. Error | Wald test p-value |
| Intercept | 1.908 | 0.2458 | <0.001 |

that is:

η = 1.908

For UTI (p-value = 0.931), the coefficient is:

|  |  |  |  |
| --- | --- | --- | --- |
|  | Estimate | Std. Error | Wald test p-value |
| Intercept | 2.303 | 0.396 | <0.001 |

that is:

η = – 2.303

For IAI (p-value = 0.350), the coefficient is:

|  |  |  |  |
| --- | --- | --- | --- |
|  | Estimate | Std. Error | Wald test p-value |
| Intercept | 2.417 | 0.279 | <0.001 |

that is:

η = – 2.417