Non-Fermentative Gram-negative Bloodstream Infection in Northern Italy: a Multicenter Cohort Study.

Renato Pascale (renato.pascale@aosp.bo.it)
Universita degli Studi di Bologna Scuola di Medicina e Chirurgia https://orcid.org/0000-0003-2687-4235

Silvia Corcione
University of Turin

Linda Bussini
University of Bologna

Livia Pancaldi
University of Bologna

Daniele Roberto Giacobbe
University of Genoa

Simone Ambretti
University of Bologna

Tommaso Lupia
University of Turin

Cristina Costa
University of Turin

Anna Marchese
University of Genoa

Francesco Giuseppe De Rosa
University of Turin

Matteo Bassetti
University of Genoa

Claudio Viscoli
University of Genoa

Michele Bartoletti
University of Bologna

Maddalena Giannella
University of Bologna

Pierluigi Viale
University of Bologna

Research article

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Abstract

Background: The management of non-fermentative gram-negative bloodstream infection (NFGN-BSI) offers numerous challenges. In this study the aim is to analyse a large cohort of patients with NFGN-BSI recruited in the northern Italy to describe epidemiology, etiological and susceptibility pattern, therapeutic management and outcome.

Methods: Multicentre retrospective cohort study of patients hospitalised at three large teaching hospitals in northern Italy in a fourth year period.

Results: 355 BSI episodes were analyzed, due to *P. aeruginosa* (72.7%), *A. baumannii* (16.6%), and *Stenotrophomonas maltophilia* (10.7%). Overall, 21.4% of isolates were defined as DTR, highest rate among *A. baumannii* (64.4%). All-cause 30-day mortality rate was 17.5%. Rates of XDR or DTR *A. baumannii* isolation were significantly higher in non-surviving patients. Independent risk factors for 30-day mortality were: age (HR 1.03, 95%CI 1.00-1.04, p=0.003), septic shock (HR 2.84, 95%CI 1.67-4.82, p<0.001) and BSI due to *Acinetobacter baumannii* (HR 2.23, 95%CI 1.27-3.94, p=0.005).

Conclusion: The overall prevalence of DTR was high in the NFGN BSI cohort analyzied, mainly among *Acinetobacter baumannii* episodes (64.4%). *Acinetobacter baumannii* is showed to be an independent predictor of mortality. These evidences marked the urgent need of new therapeutic options against this pathogen.

Trial registration number: 79/2017/O/OssN. Approved: March14th, 2017.

Background

The management of non-fermentative gram-negative bloodstream infection (NFGN-BSI) offers numerous challenges. Indeed, there are several clinical and microbiological issues that may contribute to its high morbidity and mortality. NFGN-BSI is usually diagnosed in people with severe underlying conditions, critically ill and/or immunocompromised patients [1-3] . Isolates are generally resistant, or prone to acquire resistance, to first-line antibiotics resulting in a high rate of initial inappropriate therapy and/or in the use of less effective and more toxic drugs. To counteract these findings, antibiotic combination regimens are frequently employed with controversial results in terms of efficacy, toxicity and collateral environmental damage [3, 4].

The knowledge of local epidemiology, etiological distribution in terms of causative agents and antibiotic resistance, therapeutic approach and factors associated with poor outcome are useful to guide infection control and antimicrobial stewardship policies and to inform clinicians regarding the best treatment approach [4].

With this premise, we analysed a large cohort of patients with NFGN-BSI recruited in three regions of northern Italy to describe the current epidemiology, etiological and susceptibility pattern distribution,

therapeutic management and outcome.

Methods

Study design and setting

Multicentre retrospective cohort study of patients hospitalised at three large teaching hospitals in northern Italy: i) Sant'Orsola Malpighi Hospital, Bologna; ii) City of Health and Sciences, Molinette Hospital, Turin; iii) San Martino Hospital, Genoa. The study period was from January 1st 2013 to December 31st 2016. Patients were identified through the records of the Microbiology Laboratory of each hospital.

Clinical charts and hospital records were reviewed, until 90 days after the index blood cultures (BCs), to gather study variables using a pre-established case report form. A local senior investigator systematically checked data for accuracy before they were recorded into a database. In addition, the numbers of patient days per year were recorded to assess the incidence of NFGN-BSI in the participating hospitals during the study period.

Ethic Committees of each centre approved the study, waiving of informed consent was obtained due to the retrospective non-interventional study design. Data were collected anonymously.

Participants

Inclusion criteria were all adult (≥18 years) patients diagnosed with NFGN-BSI, defined as one or more positive BCs obtained from a patient suspected of having infection. Patients were considered only once at the time of first episode (index BCs).

Exclusion criteria included: (i) polymicrobial BSI, defined as growth of more than one micro-organism, excluding potential contaminants (i.e. coagulase-negative staphylococci, Corynebacterium spp., Propionibacterium spp.); (ii) clinical data not available.

Variables and definitions

The primary outcome was all-cause mortality within 30 days after index BCs [5].

Predictor variables included: age, sex. Underlying diseases were assessed according to the Charlson comorbidity index [6]. Immunosuppression included neutropenia (neutrophil count <500/mm3), solid organ transplantation, hematopoietic stem cell transplantation, corticosteroid therapy at a dosage higher then or equivalent to prednisone 16 mg/day ≥ 15 days, uncontrolled HIV infection (<200 CD4/mm3).

BSI was classified according to the site of acquisition into nosocomial, healthcare-associated and community acquired using Friedman's criteria [7]. Clinical severity at infection onset was assessed according to SOFA score and new septic shock criteria [8]. BSI sources were established according to

Centers for Disease Control and Prevention (CDC) criteria [9]. In the absence of a recognized source, BSI was considered as primary. BSI was defined as complicated when the infection source was not fully removable.

The susceptibility pattern of isolates was classified according to Magiorakos et al. criteria [10] as non-MDR, MDR, XDR or PDR.

In addition, CDC surveillance definitions were used to assess susceptibility to carbapenems, extended-spectrum cephalosporins (ESC) and fluoroquinolones (FQ) (https://gis.cdc.gov/grasp/PSA/Downloads/AR-PhenotypeDefinitions.pdf).Moreover susceptibility to betalactam/betalactamase inhibitors (BL/BLI) and colistin was determined according to European Committee for Antimicrobial Susceptibility Testing (EUCAST) criteria.

Finally the new definition of “difficult to treat resistance” (DTR) was also assessed as reported elsewhere [11, 12] Empirical therapy was defined as antibiotics administered before the susceptibility report was available. It was considered appropriate when at least one *in vitro* active drug (according to the susceptibility pattern of the isolate) was administered within 24 h after drawing index BCs. Delayed or no active antibiotic administration within this period was considered as inappropriate empirical therapy. Definitive antibiotic therapy was defined as antibiotic treatment administered according to susceptibility results. Antibiotic regimens including more than one anti-gram-negative agents, irrespective of their *in vitro* activity against the BSI isolate, during more than 50% of treatment duration were defined as “combination regimen”. Antibiotic therapy including at least two drugs showing *in vitro* activity against the BSI isolate was labelled as “2-*in vitro* active combination regimen”. Duration of antibiotic treatment was defined as the number of consecutive days during which the patient received an appropriate antibiotic regimen. Source control was defined as the removal of the infection source within 7 days of index BCs, including the performance of non-surgical or surgical procedures to treat an obstructive focus or abscess at any site including, among others, the urinary tract, biliary tract and surgical site, and the removal of any device deemed as the source of BSI.

Microbiology

BCs were incubated using the BACTEC FX Automated Blood Culture System (Becton Dickinson, Franklin Lakes, NJ). All positive BCs were processed with Maldi Biotyper MALDI-TOF system (Bruker Daltonics, Bremen, Germany) for rapid and reliable species identification of microorganisms. Antimicrobial susceptibility testing was performed using the Vitek 2 automated system (bioMerieux, Marcy l’Etoile, France) in two hospitals (Bologna and Genova) and the MicroScan system in the remaining hospital (Torino). The minimum inhibitory concentrations (MICs) were interpreted using EUCAST clinical breakpoints for all tested antibiotics.

Statistical analysis

For the descriptive analysis, categorical variables were presented as absolute numbers and their relative frequencies. Continuous variables were presented as the mean and standard deviation if normally distributed or as the median and interquartile range (IQR) if non-normally distributed.

Risk factors for all-cause 30-day mortality were analysed by univariate and multivariate analysis. Categorical variables were compared using χ^2 or Fisher exact test when appropriate. Continuous variables were compared using the Mann–Whitney U-test. Significant and clinically relevant covariates identified in univariate analysis were introduced into a multivariable Cox regression survival model after verifying for proportional hazards and collinearity. Significance was considered for $p<0.05$. All the analysis were performed using SPSS software.

Results

Over the study period, 527 patients were diagnosed with NFGN-BSI. Of them, 172 were excluded: 146 patients had polymicrobial bacteremia, and for the remaining 26 patients clinical data were not available. Thus, 355 patients (177 from Bologna, 155 from Turin and 23 from Genova) were analysed (Figure 1).

The overall incidence of *Pseudomonas aeruginosa* BSI per 1000 patient days was 0.12, 0.12, 0.17, and 0.23 in 2013, 2014, 2015 and 2016, respectively. It was similar between participating hospitals. The overall incidence of *Acinetobacter baumannii* BSI per 1000 patient days was 0.02, 0.03, 0.06, and 0.04 in 2013, 2014, 2015 and 2016, respectively. It was similar between participating hospitals. Data shown in Figure 2.

Etiological distribution and susceptibility patterns are shown in Table 1. Most episodes were due to *P. aeruginosa* (n=258, 72.7%), followed by *A. baumannii* (n=59, 16.6%), and *Stenotrophomonas maltophilia* (n=38, 10.7%). Overall, 21.4% of isolates were defined as DTR with highest rate among *A. baumannii* (64.4%). Susceptibility rates to individual antibiotic categories are shown in Figure 3. Both *P. aeruginosa* and *A. baumannii* maintained high rate susceptibility to colistin.

The general characteristics of study population are shown in Table 2. Overall, 65.6% of patients were male, the median age was 67 (IQR 55-79) years, the median Charlson index was 5.7 (IQR 3.6-7.4), and 24.5% were immunocompromised. Most patients were hospitalized at a medical ward at BSI onset (59.2%), and the majority of episodes were hospital acquired (70.1%). Infection source was not identified in 183 (51.5%) cases, in the remaining cases the most common sources of NFGN-BSI were CVC (n=102) and lower respiratory tract (n=49).

As shown in Figure 4, data on empirical and definitive antibiotic therapy were available for 266 (75%) and 333 (94%) patients, respectively. Active therapy was administered in 35.2% and 73.8% of empiric and definitive cohort patients, respectively. Empiric combination regimens were used in 55 (15.5%) patients with a 2-*in vitro* active drugs in 16 (4.5%). Combination regimens were used in 32.4% of patients in the definitive cohort, 16.3% with 2-*in vitro* active drugs. Empiric and definitive antibiotic regimens according to isolates are shown in Supplemental Tables 1 and 2.

All-cause 30-day mortality rate was 17.5%. Relapse at 90 days was observed in 7 patients (2%) within a median of 30 days (IQR 17-50) after index BCs. Compared to patients who were alive at day 30 (Table 2), non-surviving patients exhibited higher age, Charlson index and SOFA score, and higher rate of septic shock. Rates of *A. baumannii*, XDR or DTR isolation were significantly higher in non-surviving patients, while the rates of *P. aeruginosa* isolation and empirical active therapy were higher among survivors. For definitive therapy, the use of any combination was associated with higher mortality while that of 2-*in vitro* active combination did not. At multivariate analysis adjusted for DTR, active empiric therapy, active targeted therapy and source control, the independent risk factors for all-cause 30-day mortality were: age (HR 1.03, 95%CI 1.00-1.04, p=0.003), septic shock (HR 2.84, 95%CI 1.67-4.82, p<0.001) and BSI due to *Acinetobacter baumannii* (HR 2.23, 95%CI 1.27-3.94, p=0.005).

Discussion

In our large cohort of NFGN-BSI we have found high rates of DTR and carbapenem resistance, especially among *A. baumannii*. Empirical active therapy administration was significantly higher in surviving patients at univariate analysis, however it was not confirmed at multivariate analysis. Combination therapy, also with 2 active drug, was not associated to improving surviving at multivariate analysis. Of note, *A. baumannii* isolation resulted as independent risk factors for mortality at multivariate analysis. In our cohort nosocomial infections accounted for a large majority of cases (70%), mainly CVC related and pneumonia, according to literature [13, 14]. Therefore, promote and improve infection control programs would play a critical role in reducing the rates of this kind of nosocomial infections.

The increasing importance of the NFGN bacteria is also related to their complex antimicrobial resistance profile. In our cohort carbapenem resistance showed high prevalence, with 31.8% and 64.4% rates for *P. aeruginosa* and *A. baumannii* respectively. We have also analysed the prevalence of the new definition DTR. This definition reflects the use of second-line agents with poorer therapeutic index, resulting in a better prediction of poor outcome. In our cohort, the overall prevalence of DTR was 21.1%. It varied across species being highest among *A. baumannii* BSI with rates of 64.4%. This value was much higher than data present in literature [11][15]. Similarly, DTR prevalence for *P.aeruginosa* BSI, accounted for 13.6%, higher than the rates showed previously [11][15]. As expected, in *A. baumannii* strain, CR and DTR rates were comparable.

In our study active therapy did not result statistically associated with improved outocome as previously reported elsewhere. This finding deserves further investigation. Indeed, the classical way to define if an antimicrobial agent is useful to treat an infection is the MIC determination of strains. However, MIC determination have some concerns: i) clinical laboratories cannot determine MICs with sufficient accuracy owing to the assay variation in the MIC test especially when automated or semi-automated methods are used, ii) the MIC does not represent a concentration directly compared with in vivo concentration found during treatment; iii) bacterial growth conditions in vitro could be different from those in vivo [16]. Also, the in vitro activity of antimicrobial often does not reflect the clinical feasibility due to the specific pharmacokinetic/toxicodynamic profile of the drugs and the source of infection [17].

These considerations could explain why in our cohort active therapy seems not associated to improving surviving. Similar experiences were previously reported elsewhere [18].

In our study, *A. baumannii* was an independent predictor of mortality. This is line with the characteristics of this pathogen that is commonly responsible for severe opportunistic nosocomial infections mainly in hospitalized immunocompromised patients [1-3]. Additionally, the complex antimicrobial resistance profile and the limited therapeutic arsenal for this strain may explain this result. In this scenario, polymyxins remains *in vitro* the most active agent. However, the *in vitro* activity of polymyxins not reflect the clinical feasibility due to the suboptimal pharmacokinetic/toxicodynamic profile of this class [17].

Our study has a number of limitations. Although we have analysed a large cohort of patients in three different centres, the results could be influenced by the epidemiology of a restricted area of our country. Also, our cohort is from all large tertiary teaching hospital reflecting the complexity and epidemiology of patients managed in similar institutions. The retrospective collection of patient and microbiological data could have limited integrity and accuracy. However, a senior investigator and three young investigators revised all CRFs, and reconciled data reports and missing data with the medical records before including information in the database.

To conclude, the overall prevalence of DTR was high in our NFGN BSI cohort, mainly among *Acinetobacter baumannii* episodes. Furthermore, *Acinetobacter baumannii* is showed to be an independent predictor of mortality. These evidences marked the urgent need of new therapeutic options against this pathogen.

Abbreviations

BCs : blood cultures

CDC: Centers for Disease Control and Prevention

CR: carbapenem resistance

CRFs: clinical report forms

CVC: central venous catheter

DTR: difficult to treat resistance

ESC: extended-spectrum cephalosporins

EUCAST: Eeuropean Committee for Antimicrobial Susceptibility Testing

FQ: fluoroquinolones

IQR: interquartile range

MDR: multi drug-resistant

MIC: minimal inhibitory concentration

NFGN-BSI : non-fermentative gram-negative bloodstream infection

PDR: pan drug-resistant

SOFA score: sequential organ failure assessment score

XDR: extensively drug-resistant

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committees of all hospital involved. Trial registration number of the study is 79/2017/O/OssN. The study was approved in March14th, 2017. This study used data collected from patient records while maintaining patient anonymity.

Consent for publication

Not applicable

Availability of data and materials

The original data and materials from this study are available from the corresponding author on reasonable request.

Competing interests

All authors no reported competing interests.

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Authors' contributions

RP: data analysis and drafting the manuscript, SC: data collection, LB: data collection, LP: data collection, DRG: data collection,SA: support in data collection, TL: data collection, CC: support in data collection, AM: support in data collection, CV: support in study design, FGDR: support in study design,MB: manuscript revision ,MG: study design, data analysis and manuscript revision,PV: study design and manuscript revision

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Not applicable

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Tables

Table 1: Causative agents and their susceptibility patterns of monomicrobial NFGN-BSI during 2013-2016 in three tertiary teaching hospitals from northern Italy*.

	N	MDR	XDR	PDR	CR	DTR
Pseudomonas aeruginosa	258	15 (5.8)	53 (20.5)	/	82 (31.8)	35 (13.6)
Acinetobacter baumannii	59	0	37 (62.7)	1(1.7)	38 (64.4)	38 (64.4)
Stenotrophomonas maltophilia	38	/	/	/	1(2.6)	2 (5.3)

*Resistance categories (MDR, XDR, PDR) were mutually exclusive while antibiotic class resistances (CR) and new definition (DTR) were not.

Abbreviations: CR carbapenem resistance; DTR difficult-to-treat resistance; MDR multidrug-resistance; PDR pandrug-resistance, XDR extensively drug-resistance.

Table 2. Univariate analysis of risk factors for all-cause 30-day mortality

	Total N= 355 (%)	Survivors N= 293 (%)	Non-survivors N= 62 (%)	*p*
Demographics				
Age (years) (median, IQR)	67 (55-79)	67 (54-78)	73 (61-84)	0.016
Male sex	233 (65.6)	194 (66.2)	39 (62.9)	0.66
Comorbidities				
Charlson index (median, IQR)	5.7 (3.6-7.4)	5.2 (3.5-7.1)	6.25 (4-9)	0.034
Immunosuppression	87 (24.5)	74 (25.3)	13 (21)	0.52
Ward of admission				0.22
Medical	210 (59.2)	176 (60.1)	34 (54.8)	
ICU	80 (22.5)	61 (20.8)	19 (30.6)	
Surgical	65 (18.3)	56 (19.1)	9 (14.5)	
Site of BSI acquisition				0.078
Community acquired	71 (20.0)	65 (22.2)	6 (9.7)	
Healthcare associated	35 (9.9)	27 (9.2)	8 (12.9)	
Hospital acquired	249 (70.1)	201 (68.6)	48 (77.4)	
CRE carrier at BSI onset	44 (12.1)	35 (11.9)	9 (14.5)	0.462
Clinical severity at BSI onset				
SOFA (median, IQR)	3 (2-5)	3 (2-5)	4 (3-6)	0.005
Septic shock	59 (16.6)	38 (13)	21 (33.9)	0.001
Source of BSI				
Undefined	183 (51.5)	150 (51.2)	33 (53.2)	0.782
CVC related	102 (28.7)	86 (29.4)	16 (25.8)	0.645
Lower respiratory tract	49 (13.8)	39 (13.3)	10 (16.1)	0.686
Biliary tract	41 (11.5)	34 (11.6)	7 (11.3)	1

Urinary tract	31 (8.7)	27 (9.2)	4 (6.5)	0.624
Intra-abdominal	18 (5.1)	16 (5.5)	2 (3.2)	0.551
Complicated BSI	38 (10.7)	27 (12.9)	11 (21.6)	0.125
Etiology				0.009
Pseudomonas aeruginosa	258 (72.7)	222 (75.8)	36 (58.1)	0.005
Acinetobacter baumannii	59 (16.6)	41 (14)	18 (29)	0.005
Stenotrophomonas maltophilia	38 (10.7)	30 (10.2)	8 (12.9)	0.651
Resistance phenotypes*				0.005
MDR	34 (9.6)	22 (8.4)	12 (22.2)	
XDR	58 (16.3)	46 (17.5)	12 (22.2)	
Antibiotic class resistance*				
ECR	95 (26.7)	77 (26.3)	18 (29)	0.752
BL/BLIR	78 (22)	55 (18.8)	23 (37.1)	0.002
CR	124 (34.9)	93 (31.7)	31 (50)	0.008
FQR	144 (40.6)	107 (36.5)	37 (59.7)	0.001
AminoglycosidesR	98 (27.6)	69 (26.4)	29 (51.8)	<0.001
TMP/SMXR	53 (14.9)	39 (21.9)	14 (29.2)	0.337
COLIR	5 (1.4)	5 (1.7)	0 (0)	0.592
New definition*				
DTR	75 (21.1)	52 (17.7)	23 (37.1)	0.001
Therapeutic management				
ID Consultation	148 (41.7)	119 (40.6)	29 (46.8)	0.397
Source control	131 (36.9)	111 (37.9)	20 (32.3)	0.470
Appropriate empirical therapy	125 (35.2)	111 (38.4)	14 (23.7)	0.037
Combination empirical therapy	55 (15.5)	42 (18.9)	13 (29.5)	0.152
2 *in vitro* active combination empirical therapy	16 (4.5)	16 (12.8)	0	0.223

Appropriate definitive therapy	262 (73.8)	222 (76.8)	40 (67.8)	0.184
Combination definitive therapy	115 (32.4)	89 (32)	26 (47.3)	0.031
2 *in vitro* active combination definitive therapy (with drugs)	58 (16.3)	48 (20.7)	10 (23.8)	0.682

* Resistance categories were mutually exclusive while antibiotic class resistances and new definition (DTR) were not.

Abbreviations: BL/BLIR betalactam/betalactamase inhibitor resistance; BSI bloodstream infection; COLIR Colistin resistance, CR carbapenem resistance; CRE carbapenem-resistant Enterobacteriaceae; CVC central venous catheter; DTR difficult-to-treat resistance; ECR extended-spectrum cephalosporin resistance; FQR fluoroquinolone resistance; ICU intensive care unit; IQR interquartile range;ID Consultation Infectious Disease Consultation, MDR multidrug-resistance;; SOFA sequential organ failure assessment; TMP/SMXR Trimethoprim/sulfamethoxazole resistance, XDR extensively drug-resistance.

Figures

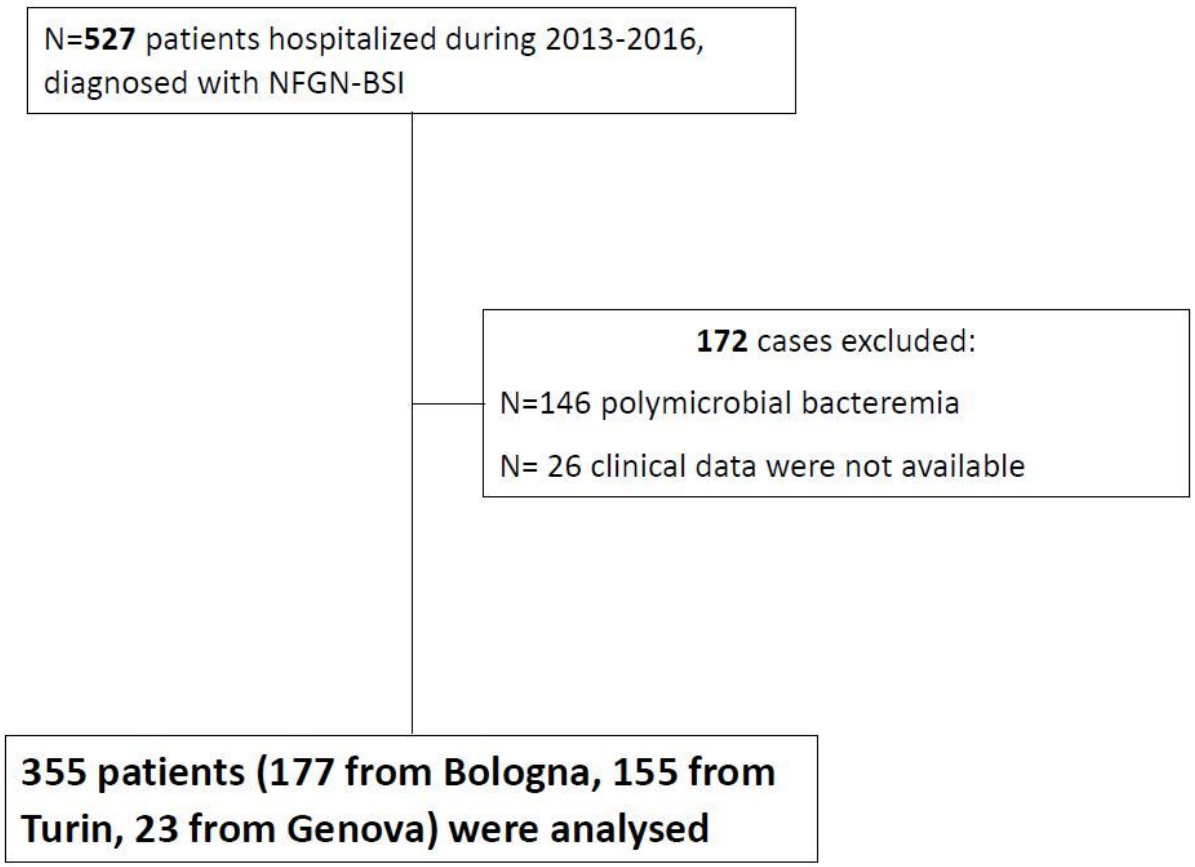

Figure 1

Flow diagram of study population.

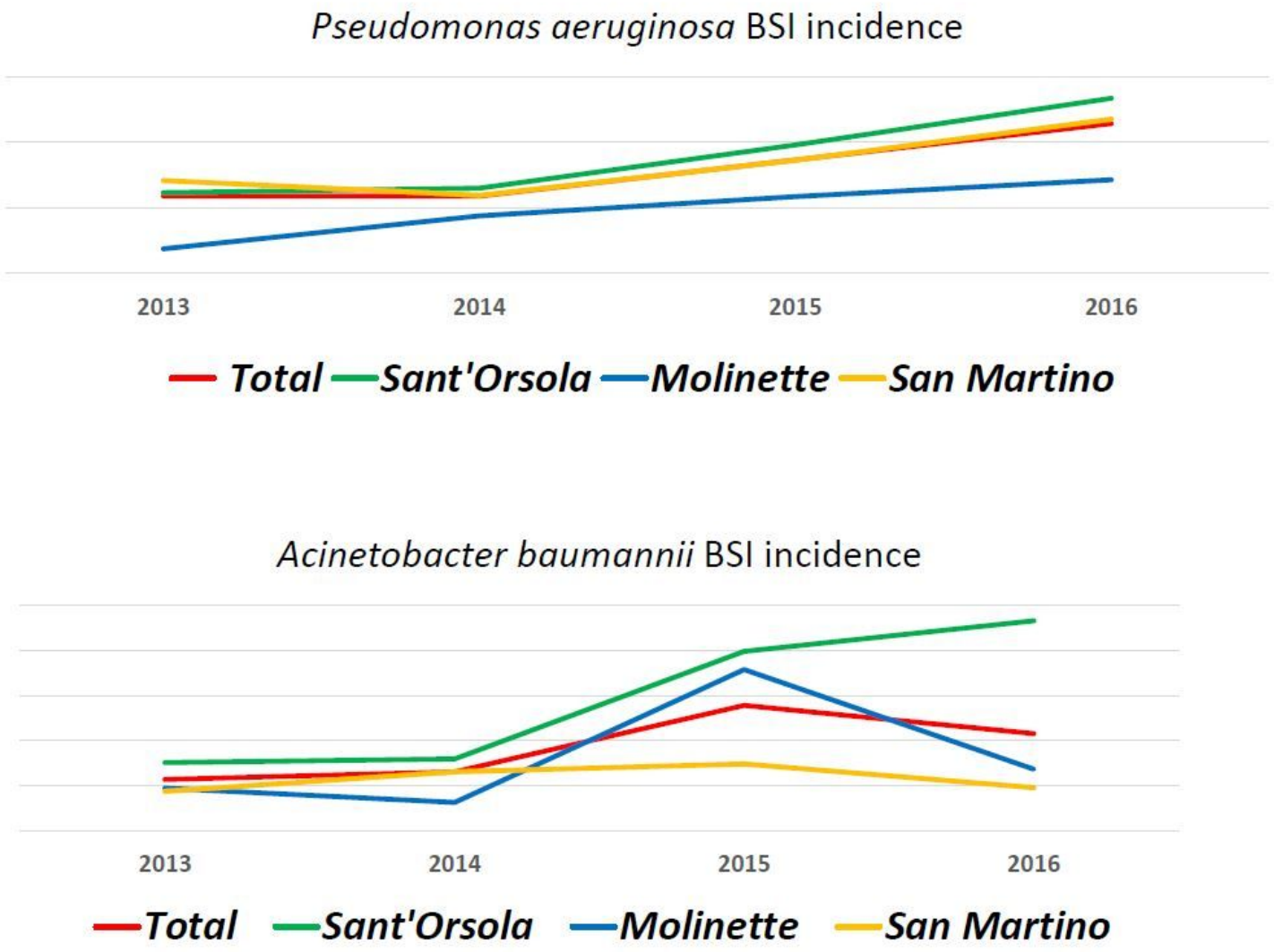

Figure 2

Overall incidence of P. aeruginosa and A. baumannii BSI per 1000 patient days between 2013-2016 years.

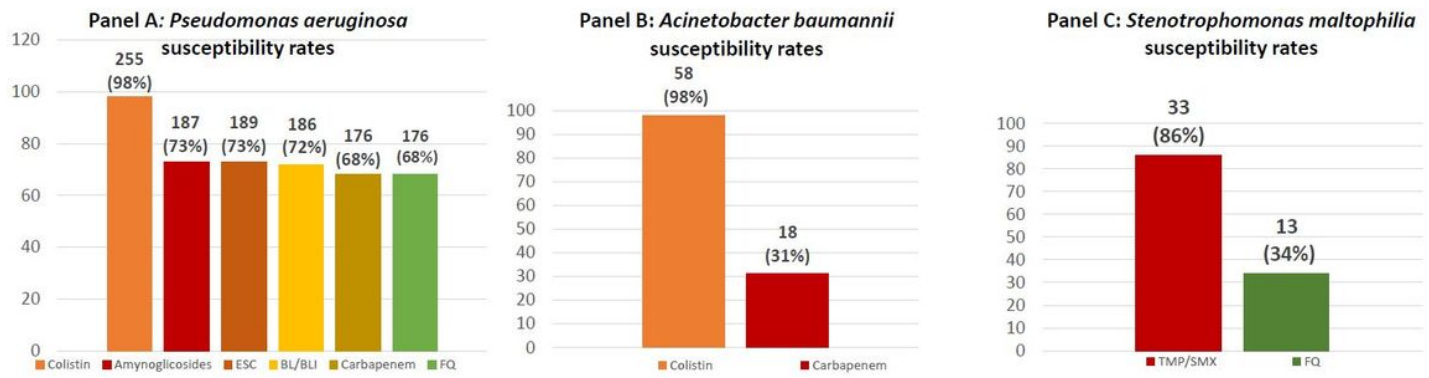

Figure 3

Susceptibility rates to individual antibiotic categories for Pseudomonas aeruginosa, Acinetobacter baumannii and Stenotrophomonas malptophilia. Abbreviations: BL/BLI betalactam/betalactamase inhibitor, ESC extended-spectrum cephalosporin, FQ fluoroquinolone resistance;

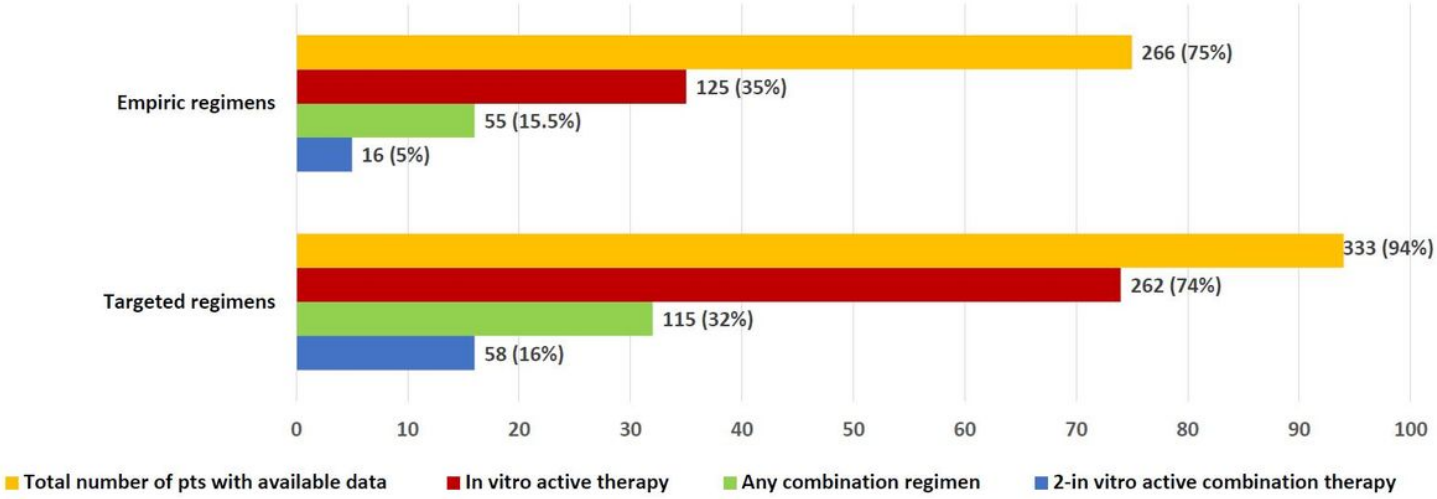

Figure 4

Antibiotic management of NFGN-BSI.

Supplementary Files

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- TablesAdditional.docx