Multi-drug-resistant gram-negative bacterial infection in surgical patients hospitalized in the ICU: a cohort study

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Introduction

- Mortality and prolonged hospitalization among patients who have been submitted to major surgical operations is often attributed to infections that occur in the early postoperative period
- Considerable change in the epidemiology of hospital acquired infections
- Multi-drug-resistance (MDR) defined as resistance to all but 3 classes of antibiotics
- We sought to investigate factors that have been related to the development of resistance to antibiotics and attribute mortality and length of hospital stay of patients with such infections to the resistance pattern of the pathogen or to the various other comorbidity conditions and complicating factors.

•Klevens RM et al. Hospitals, 2002. Public Health Rep 2007, 122:160-166.
•Richards MJ. Infect Control Hosp Epidemiol. 2000, 21(Suppl 8):510-515
•Falagas ME et al. BMC Infect Dis. 2005, 5:24.

Methods

Retrospective cohort study at a general, 450-bed, tertiary-care hospital in Athens, Greece.

- Patients hospitalized in the ICU for more than 5 days following general surgical operations during a 7 year period from the first day of hospital operation, in November 2001, to May 2007
- Patients without any infection on ICU admission.
- Cases of infection included were clinically and microbiologically documented
- Patients who had a clinical infection that was not microbiologically documented were eliminated from the study.
- Patients who had an infection, caused by MDR-GNB, assigned to the case group (group A). The rest in the comparison group (group B).
- Secondary comparison with patients who did not develop any infection (sub-group B1)

Methods

- The Center for Disease Control and Prevention definitions were used to determine nosocomial infection
- The outcomes of this cohort were all-cause in-hospital mortality, mortality attributed to infection caused by the studied isolates, infection outcome, and total length of hospital and ICU stay.
- Recorded demographics, medical history and comorbidity, susceptibility to antimicrobials, date of culture, type of specimen, invasive procedures, outcomes, antimicrobials type and duration of treatment, transfusion of blood products, renal replacement therapy, antineoplastic, immunosuppressive or immunomodulating therapies, invasive procedures, surgical intervention type, classification, perioperative antimicrobial prophylaxis, operative time, electivity, haemostatic packing, material placement, and reoperation, APACHE II score

Methods

- The chi square and Fisher's exact tests were used to compare groups for dichotomous variables, as appropriate. The t-test and the Mann-Whitney signed-rank test were used to compare groups for normally and non-normally distributed continuous variables, respectively.
- Variables found to be significantly associated with the development of infection caused by MDR-GNB, in the bivariable analyses, were entered in a multivariable forward, stepwise, logistic regression model and the adjusted odds ratio (OR) and 95% confidence intervals (CIs) were calculated.
- Variables' colinearity was tested. Tolerance <0.1 indicated that the variable was redundant and highly correlated with other variables that were already in the model. Summary measures of goodness of fit were performed using the Hosmer-Lemeshow test.

Results–study population

- 100 patients (54 males)
- Mean age of the study population was 67 years (range 22-92)
- Mean length of hospital stay was 29 days (range 9-98)
- Mean length of ICU stay was 16 days (range 6-55)
- Mean APACHE II score at first ICU admission was 16 (range 4-33).
- Mean total operative time was 278 minutes (range 45-665) and 42% reoperated.
- colorectal (38%), small bowel (19%), stomach (9%), liver (9%), pancreas (6%), and other general surgical operations (19%)
- 48 MDR-GNB infections (32 Acinetobacter baumannii, 8 Pseudomonas aeruginosa, 8 Klebsiella pneumoniae (group A)

Results-study population

- 14 patients had infections by gram-positive bacteria (5 Streptococcus faecalis, 3 Staphylococcus aureus, 6 other gram-positive pathogens)
- 6 had infections caused by gram-negative bacteria susceptible to more than 3 of the tested antibiotics (5 cases of Pseudomonas aeruginosa and 1 case of Klebsiella pneumoniae)
- 2 patients who had infections caused by Candida albicans.
- 30 patients that did not have any clinically diagnosed nosocomial infection during hospitalization.
- 14 cases of multi-microbial infections (23% of infections were mulitmicrobial). In all multi-microbial infections an MDR-GNB was isolated and patients were assigned to Group A.
- 43% of infections respiratory tract, 24% abdominal, 17% blood stream, 9% catheter related and 7% in other sites.

Results-univariate analysis

- Reoperation and total operative time were significantly higher in group A compared to group B (54.2% v 30.8% p=0.025, mean 333.3 v 228.8 minutes p<0.001, respectively).
- Total operative time, and rates of contaminated surgery were significantly higher in group A compared to sub-group B1 (mean 333.3 v 221.4 minutes p<0.001, 72.9% v 46.7% p=0.03, respectively).
- Mean mechanical ventilation duration, mean tracheostomy duration, rates of blood transfusion, and special treatments were significantly higher in group A compared to group B (7.8 v 4.5 days p=0.033, 2.6 v 0.6 days p=0.009, 91.7% v 67.3% p=0.003, 52.1% v 28.8% p=0.025, respectively).
- Mean tracheostomy duration, rates of renal replacement therapy and blood transfusion were significantly higher in group A compared to sub-group B1 (2.6 v 0.7 days p=0.031, 33.3% v 10% p=0.029, 91.7% v 66.7%).

Results-univariate analysis

- Prior antibiotics use (within last 3 months) differed significantly when comparing group A to sub-group B1 (mean 43.8 v 16.7 days, p=0.015).
- Group A had received significantly longer metronidazole, anti-pseudomonal penicillins, carbapenems, and linezolid therapy (up to the day of infection) compared to patients of group B (mean duration of 10.1 v 6.5 days p=0.027, 5.1 v 3 days, p=0.007, 8.9 v 3.5 p<0.001, 3.6 v 1.1 p<0.001, respectively).
- Mean cumulative days of antibiotic treatment and total days of antibiotic treatment were significantly more in group A compared to group B (57.1 v 34.6 days p<0.005, and 16.6 v 11.6 days p=0.022, respectively).
- Group A had received significantly longer carbapenems and linezolid therapy (up to the day of infection) compared to patients of group B1 (mean duration of 8.9 v 4.1 days p<0.003, and 3.6 v 1.7 days p=0.031, respectively).

Results-univariate analysis

- Admission to the hospital in the first year of hospital operation was considerably less frequent among patients of group A (12.5%) compared to group B (38.5%, p=0.006) and group B1 (46.7%, p=0.001).
- Regarding other studied outcomes, group A had lower survival rate (37.5%) compared to group B (53.8%, not statistically significant) and sub-group B1 (63.3%, p=0.036). Group A had higher mean total length of hospital and ICU stay (34.6 and 19.4 days, respectively) compared to group B (24 and 13.1 days, p=0.01 and 0.04, respectively) and sub-group B1 (21.9 and 11.9 days, p=0.01 and 0.03, respectively).
- Death was attributed to infection in 70% of group A patients who died.

Results multivariate analysis

Table 2. Forward multivariable logistic regression model for infection caused by muti-drug-resistant gram-negative bateria (MDR-GNB) (dependent variable). Comparison of patients that developed infection caused by MDR-GNB (n=48) (group A) with patients that did not (n=52) (group B).

Variables in the equation	Adjusted odds ratio (95% CIs)	Clinical meaning	p value
Total operative time, minutes	1.007 (1.003-1.011)	For every minute of surgery, patients' odds to acquire an infection caused by MDR-GNB increased by 0.7%	**0.001**
Special treatments during hospitalization (antineoplastic, immunosuppressive or immunomodulating therapies)	8.9 (1.8-17.3)	Special treatments increased patients' odds to acquire an infection by MDR-GNB by 8.9 times	**0.004**
Metronidazole use duration, days	1.09 (1.04-1.18)	For every day of metronidazole use, patients' odds to acquire an infection caused by MDR-GNB increased by 9%	**0.039**
Carbapenems use duration, days	1.09 (1.01-1.18)	For every day of carbapenems use, patients' odds to acquire an infection caused by MDR-GNB increased by 9%	**0.023**
Admission in years 2002 (first year of hospital operation)	0.1 (0.03-0.43)	Patients admitted during the first year of hospital operation had decreased odds to acquire an infection caused by MDR-GNB by 10 times	**0.002**

Results multivariate analysis

Table 3. Forward multivariable logistic regression model for infection caused by muti-drug-resistant gram-negative bateria (MDR-GNB) (dependent variable). Comparison of patients that developed infection caused by MDR-GNB (n=52) (group B) with patients that did not develop any infection (n=30) (sub-group B1).

Variables in the equation	Adjusted odds ratio (95% CIs)	Clinical meaning	p value
Total operative time, minutes	1.007 (1.003-1.011)	For every minute of surgery, patients' odds to acquire an infection caused by MDR-GNB increased by 0.7%	**0.001**
Prior antibiotics use (within 3 months prior to admission)	3.8(1.07-13.2)	Prior antibiotics use increased patients' odds to acquire an infection caused by MDR-GNB by 3.8 times	**0.002**
Admission in years 2002 (first year of hospital operation)	0.07 (0.01-0.4)	Patients admitted during the first year of hospital operation had decreased odds to acquire an infection caused by MDR-GNB by 14 times	**0.03**

Discussion-main findings

- MDR-GNB infection is independently associated with:

✓ the total operative time

✓ special treatments during hospitalization (antineoplastic, immunosuppressive or immunomodulating therapies)

✓ carbapenems and metronidazole use duration

✓ prior antibiotics use (within 3 months prior to admission).

✓ The above were adjusted for timely distribution of infection that was found to be significantly different

Discussion - Limitations

- Innate limitations of retrospective studies
- Certain cases of colonization may have been treated as clinical infections.
- Only one incidence per patient was analysed.
- Inclusion criteria ruled off patients with benign clinical course, and, thus, conclusions may not apply to the majority of patients treated in the general surgery department.
- Relatively limited number of cases included in this analysis did not permit to follow the “rule of thumb” in a backwards stepwise logistic regression model (a minimum of 10 binary events per candidate variable inserted in the multivariable model)


Thank you for your attention