Original Article

Mortality among Patients with Nosocomial Infections in Tertiary Intensive Care Units of Sahloul Hospital, Sousse, Tunisia

Mohamed Ben Rejeb MD•[1], Jihene Sahli MD[1], Dhekra Chebil MD[1], Selwa Khefacha–Aissa MD[1], Nadia Jaidane MD[1], Balsam Kacem MD[1], Houssem Hmouda MD[2], Lamine Dhidah MD[1], Houyem Said-Latiri MD[1], Walid Naija MD[3]

Abstract

Background: Nosocomial infections are public health issues that are associated with high mortality in intensive care units. This study aimed to determine nosocomial infection-associated mortality in Tunisian intensive care units and identify its risk factors.

Methods: A prospective cohort study was carried out in intensive care units of a Tunisian University Hospital. The ICUs-wide active surveillance of nosocomial infections has been performed between 1 July 2010 and 30 June 2011. Data collection was based on Rea-Raisin protocol 2009 of "Institut National de Veille Sanitaire" (InVS, Saint Maurice - France). We used Kaplan Meier survival analysis and Cox Proportional Hazard regression to identify independent risk factors of nosocomial infection-associated mortality.

Results: Sixty-seven patients presented nosocomial infection in the end of the surveillance. The mean age of patients was 44.71 ± 21.2 years. Of them, 67.2% were male and 32.8% female. Nosocomial bacteremia was the most frequent infection (68.6%). Nosocomial infection-associated mortality rate was 35.8% (24/67). Bacteremia (Hazard Ratio (HR)) = 3.03, 95% Confidential Interval (95% CI): [1.23 – 7.45], *P* = 0.016) and trauma (HR = 3.6, 95% CI: [1.16 – 11.2], *P* = 0.026) were identified by Cox regression as independent risk factors for NI-associated mortality.

Conclusions: Our rate was relatively high. We need to improve the care of trauma patients and intensify the fight against nosocomial infections especially bacteremia.

Keywords: Intensive care unit, mortality, nosocomial infection, risk factor

Cite this article as: Rejeb MB, Sahli J, Chebil D, Khefacha–Aissa S, Jaidane N, Kacem B, Hmouda H, Dhidah L, Said-Latiri H, Naija W. Mortality among patients with nosocomial infections in tertiary intensive care units of Sahloul hospital, Sousse, Tunisia. *Arch Iran Med*. 2016; **19(3):** 179 – 185.

Introduction

Nosocomial infections (NI) are common adverse events in healthcare[1] and they are more severe in high technology hospital units harboring critically ill patients needing intensive life support.[2,3] Patients in intensive care unit (ICU) are at a higher risk of developing NI than other patients.[4] High frequency of NI in those units is associated with considerable morbidity, mortality and significant excess costs.[5–7] ICU mortality rate varies between 9 and 38% of which 60% could be due to NI.[8]

Estimation of mortality in ICU and particularly among patients with NI is an important indicator of care quality in these units. Moreover, controlling NI prognosis factors is important to reduce NI-associated mortality. However, according to World Health Organization (WHO), 66% (97/147) of developing countries have no published data on the burden of NI at all.[9] The limited number of studies with a broad scope and the lack of national surveillance systems hamper any attempts to estimate the burden of NI at country or regional level in low-and middle-income countries[9] such as Tunisia. Thus, an epidemiological surveillance of NI was carried out in ICUs in our organization. Generated data could explain ICU-NI mechanisms, identify risk factors, estimate mortality and determine prognosis factors. This allows us to place strategic planning in order to reduce morbidity and mortality in our ICUs. In the present study, we were interested to examine NI-associated mortality rate and determine prognosis factors among patients with NI in ICUs.

Authors' affiliations: [1]Department of Prevention and Care Safety, Hospital of Sahloul, Route Ceinture Sahloul, Sousse, Tunisia, [2]Department of Medical Intensive Care, Hospital of Sahloul, Route Ceinture Sahloul, Sousse, Tunisia, [3]Department of Surgical Intensive Care, Hospital of Sahloul, Route Ceinture Sahloul, Sousse, Tunisia.

•**Corresponding author and reprints:** Mohamed Ben Rejeb MD, Department of Prevention and Care Safety, Hospital of Sahloul, Route Ceinture Sahloul, Sousse 4054, Tunisia. Tel: +216-54-098-709, Fax: +216-73-367-451, E-mail: mohamed_benrejeb@yahoo.fr, mohamed.benrejeb@rns.tn.

Accepted for publication: 24 November 2015

Patients and Methods

Design and setting

This is prospective cohort study carried out between 1 July 2010 and 30 June 2011 in a 630-beds public tertiary care hospital of Sahloul (Sousse) in Eastern Tunisia with 28079 admissions and 199497 hospitalization-days in 2010. This study was conducted in the surgical ICU (SICU) with 26 beds and medical ICU (MICU) with 5 beds. In 2010, the annual number of admissions was 545 and 83 respectively and the number of hospital days was 7741 and 1301 respectively.

Study patients

All patients hospitalized for more than 48 hours in the ICUs (Date of discharge from ICU ≥ Entry date + 2 days) and developing a NI were included in this study. We excluded patients with an ICU stay less than 48 hours and those who died following an infection upon admission to ICU.

Definitions of Variables

NIs were diagnosed according to the definitions of « Comité

Technique des Infections Nosocomiales et les Infections Liées aux Soins" (CTINLIS, France). NI was defined as an infection not present or incubating at admission to the ICU and occurred at least 48 h after admission to the ICU.[10] NI-associated Mortality was defined as crude mortality in patients with NI.[11] We considered the survival variable as the duration of post-infection following up in days (Date of discharge from ICU – Date of infection).

Data collection

Data collection was based on Rea-Raisin protocol 2009 of "Institut National de Veille Sanitaire" (InVS, Saint Maurice - France).[11] Collected data included patient risk related factors (age, gender, Simplified Acute Physiology Score II (SAPS II), prior exposure to antimicrobials (was defined as the administration of antibiotics for more than 48 h within 60 days preceding NI), admission diagnosis (trauma, surgical, medical), immunosuppression, infection upon admission to ICU, type of ICU and length stay in ICU, use of invasive devices (intubation and mechanical ventilation, central venous catheterization (CVC), urinary catheterization (presence or absence, start date, end date)) and infection (pneumonia, colonization and/or infection of central venous catheters, bacteremia, and urinary tract infection (date of onset, antibiotic therapy and microorganisms)).

Ethical considerations

This study was approved by local Ethics Committee. Every piece of information related to the identity of the patients stayed confidential.

Statistical analysis

Data analysis was performed using SPSS for Windows 19.0. Continuous variables were described as means ± standard deviations. Categorical variables were summarized with absolute and relative frequencies. To compare Kaplan Meier curves, Log rank test was used. Kaplan-Meier survival analysis and Cox regression were used to calculate the Hazard Ratio (HR) of acquiring infection for patient characteristics with regard to the time at risk. Risk factors with a *P*-value of 0.20 or less in the univariate regression were initially included in the Cox regression models. The model was reduced by means of manual backward elimination. Statistical significance was defined at $P \leq 0.05$.

Results

Overall, 91 NI were identified in 67 patients. Nosocomial bacteremia (NB) was the most frequent infection (68.6%). The mean age of patients was 44.71 ± 21.2 years. Of them, 67.2% were male and 32.8% female. The mean SAPS II on admission was 33.2 ± 17.5. The use of devices was noticed in 95.5%, 76.1% and 71.6% respectively for urinary catheter, endotracheal tube and central venous catheter. Table 1 illustrates the characteristics of the study population. During this study, 24 patients died. NI-associated mortality rate was 35.8%. The median survival was 44.8 ± 7.5 days (95% CI: [30-59.5]) (Figure 1). Specific mortality rates, according to the infectious site were 38.9%, 33.3% and 43.5% respectively for nosocomial pneumonia (NP), urinary tract nosocomial infection (UTI) and NB (Table 2). In univariate analysis, no significant associations between mortality and all studied factors were detected (Table 2). However, bacteremia (adjusted HR = 3.03, 95% IC: [1.23 – 7.45], $P = 0.016$) and trauma (adjusted HR = 3.6, 95% CI: [1.16 – 11.2], $P = 0.026$) were identified by Cox regression as independent risk factors for NI-associated mortality (Table 3).

Discussion

The modern evidence-based approach to infection prevention and control clearly emphasizes that no type of health-care facility in any country can claim to be free from the risk of NI. However, the risk of NI is significantly higher in ICUs, with approximately 30% of patients affected by at least one episode of NI with substantial associated morbidity and mortality.[9] Data on the mortality indicator is difficult to retrieve as it requires complex evaluation, particularly to confirm that death is directly linked to NI episodes and not to other factors.[9] Estimating the excess mortality due to NI is challenging, especially in high-risk patients who are at greater risk of death because of severe underlying and intricate diseases and they may be in terminal phase of their illness.[12] In this context, it is imperative to distinguish between NI-associated mortality and mortality attributable to NI. Any mortality associated with NI will be in addition to the mortality associated with the underlying disease process. Attributable mortality is defined as the total mortality minus the mortality associated with the underlying disease process and can be estimated by using specific models.[13]

In our study, mortality rate was 35.8% (24/67). The mortality rate in patients with NI varies between studies. In studies mainly conducted in high-income countries, crude mortality rates associated with NI vary from 12% to 80%.[5] However, the analysis and the comparison of NI and its associated mortality rates are complicated by the differences between the diagnostic techniques used and the studied populations. The NI-associated mortality is largely influenced by the affected population, the diagnostic strategy, time to diagnosis, time before initiation of antibiotic therapy, the causal organism and effectiveness of initial antibiotic therapy.[14] Our rate was significantly higher than those reported by several studies in high income countries which were estimated between 5.8% and 33.5%.[1,15,16] Nevertheless, it remains well below those found in developing countries. Indeed, the rates vary between 17.2% and 69%.[6,17,18] The different rates are illustrated in Table 4. In this study, specific mortality rates, according to the infectious site were 38.9%, 33.3% and 43.5% respectively for NP, UTI and NB. As overall mortality rate, specific rates were variable in the literature. In high income countries, mortality rates vary between 8.9% and 47% in case of NP or ventilator associated pneumonia (VAP),[19–23] between 10.9 and 51% for NB,[19–22] and between 2.3 and 42% for UTI.[19,20,22] However, they are much higher in developing countries with a variation of 38.5 to 71.5% for NP,[24,25] 26.7% to 62.5% for NB,[24–26] and 18.5 to 42.9% for UTI.[24,25] Table 5 reports this cross-countries variation of specific mortality rate by site of infection in the ICU.

Prevention of the ICU-NI demands knowledge of the infection rates, sources, types, and risk factors of infection, as well as associated mortality. In our study, an admission diagnosis of trauma (*vs.* medical and surgical) was a predictor of mortality. Traumatized were three times more likely to die than non-trauma patients. This high risk was reported by Myny, et al.[27] They studied predictors of mortality in patients with VAP. However, most studies showed no significant relationship between admission diagnosis and death.[21,23,26,28] Differences between studies may be related to different patient recruitment which determines the nature of pathologies. Certain ICUs support more the head injured patients

Table 1. Characteristics of patients with NI in ICUs

Characteristic	Number (n)	Percentage (%)
Age		
< 65 years	55	82
≥ 65 years	12	12
Gender		
Male	45	67.2
Female	22	32.8
SAPS-II		
≤ 40	43	64.2
> 40	24	35.8
Immunosuppression		
Yes	13	19.4
No	54	80.6
Infection upon admission to ICU		
Yes	14	21
No	53	79
Prior exposure to antibiotics		
Yes	13	19.4
No	54	80.6
Surgery		
Yes	15	22.4
No	52	77.6
Trauma		
Yes	32	47.5
No	35	52.5
Duration of endotracheal intubation		
0 days	16	23.9
1–10 days	23	34.3
> 10 days	28	41.8
Tracheotomy		
Yes	13	19.4
No	54	80.6
Re-intubation		
Yes	7	10.4
No	60	89.6
Duration of urinary catheter		
0 days	3	4.5
1–6 days	11	16.4
> 6 days	53	79.1
Duration of central venous catheter		
0 days	19	28.4
1–7 days	5	7.5
> 7 days	43	64.2
Pneumonia		
Yes	36	53.7
No	31	46.3
Bacteremia		
Yes	46	68.7
No	21	31.3
Urinary tract infection		
Yes	9	13.4
No	58	86.6
ICU		
Surgical	59	88.1
Medical	8	11.9

ICU: Intensive care unit; SAPS-II: Simplified Acute Physiology Score II

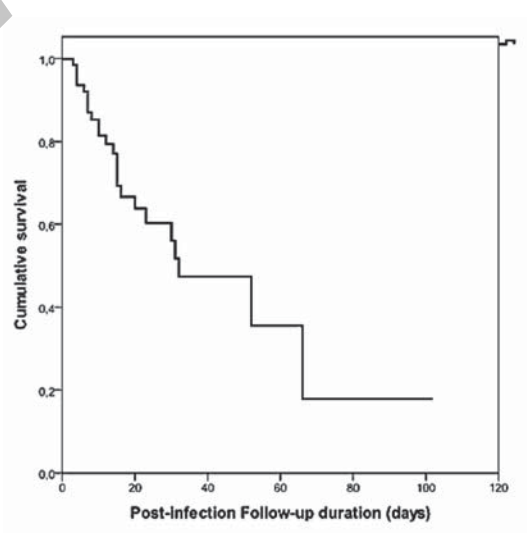

Figure 1. Kaplan-Meier survival curve of patients with nosocomial infections in intensive care units of Sahloul hospital (Sousse, Tunisia) in 2010–2011. Median survival: 44.8 ± 7.5 days (95% CI: [30 – 59.5]).

Table 2. Univariate analysis of risk factors of mortality in patients with NI in ICUs

Factor	Died (%), (n = 24)	Survivors (%), (n = 43)	HR [95%CI]	*P*
Age			1.56 [0.61–4]	0.35
≥ 65 years	6 (50)	6 (50)		
< 65 years	18 (32.7)	37 (67.3)		
Gender			0.74 [0.32–1.7]	0.48
Male	15 (33.3)	30 (66.7)		
Female	9 (40.9)	13 (59.1)		
SAPS-II			2.08 [0.93–4.62]	0.08
> 40	12 (50)	12 (50)		
≤ 40	12 (27.9)	31 (72.1)		
Immunosuppression			0.93 [0.3–2.75]	0.87
Yes	4 (30.8)	9 (69.2)		
No	20 (37)	34 (63)		
Infection upon admission to ICU			1.59 [0.65–3.87]	0.33
Yes	7 (50)	7 (50)		
No	17 (32.1)	36 (67.9)		
Prior exposure to antibiotics			0.88 [0.38–2]	0.77
Yes	5 (38.5)	8 (61.5)		
No	19 (35.2)	35 (64.8)		
Surgery			0.67 [0.25–1.8]	0.43
Yes	5 (33.3)	10 (66.7)		
No	19 (36.5)	33 (63.5)		
Trauma			2.23 [0.94–5.28]	0.07
Yes	15 (46.9)	17 (53.1)		
No	9 (25.7)	26 (74.3)		
Duration of endotracheal intubation				
0 days	6 (37.5)	10 (62.5)	1	- - -
1–10 days	7 (30.4)	16 (69.6)	0.99 [0.33–3]	0.98
>10 days	11 (39.3)	17 (60.7)	0.75 [0.27–2]	0.57
Tracheotomy			0.69 [0.27–1.78]	0.69
Yes	6 (46.2)	7 (53.8)		
No	18 (33.3)	36 (66.7)		
Re-intubation			0.82 [0.24–2.8]	0.75
Yes	3 (42.9)	4 (57.1)		
No	21 (35)	39 (65)		
Duration of urinary catheter				
0 days	1 (33.3)	2 (66.7)	1	- - -
1–6 days	4 (36.4)	7 (63.6)	1.57 [0.17–14.4]	0.68
> 6 days	19 (35.8)	34 (64.2)	0.90 [0.12–6.9]	0.92
Duration of central venous catheter				
0 days	6 (31.6)	13 (68.4)	1	- - -
1–7 days	1 (20)	4 (80)	1.08 [0.13–9.24]	0.94
> 7 days	17 (39.5)	26 (60.5)	0.99 [0.38–2.6]	0.99
Pneumonia			1.1 [0.49–2.5]	0.8
Yes	14 (38.9)	22 (61.1)		
No	10 (32.3)	21 (67.7)		
Bacteremia			2.35 [0.85–7.5]	0.09
Yes	20 (43.5)	26 (56.5)		
No	4 (19)	17 (81)		
Urinary tract infection			0.39 [0.09–1.7]	
Yes	3 (33.3)	6 (66.7)		
No	21 (36.2)	37 (63.8)		
ICU			1.18 [0.25–6.61]	0.65
Surgical	22 (37.3)	37 (62.7)		
Medical	2 (25)	6 (75)		

ICU: Intensive care unit; SAPS-II: Simplified Acute Physiology Score II; HR: Hazard Ratio; 95% CI: 95% Confidential interval

Table 3. Multivariate analysis of risk factors of NI-associated mortality in ICUs

Factor	Adjusted HR	95%CI	*P*
Trauma	3.03	[1.23–7.45]	0.016
Bacteremia	3.6	[1.16–11.2]	0.026
HR: Hazard Ratio; 95% CI: 95% Confidential Interval.			

Table 4. Cross-countries variation of NI-associated Mortality rates in ICUs

Author	Country	ICU	Years	Infected patients (n)	Mortality rate (%)
Klevens[1]	USA	Surgical and medical	1990–2002	1.7 millions	5.8
Ylipalosaar[15]	Finland	Surgical and medical	2002–2003	80	25.7
Januel[16]	France	Surgical and medical	1995–2003	1677	33.5
Dasgupta[17]	India	Surgical and medical	2012	29	17.2
Chen[6]	Taiwan	Surgical and medical	1996–1997	86	33.3
Cevik[18]	Turkey	Neurological	2001–2002	74	69
Our study	Tunisia	Surgical and medical	2010–2011	67	35.8

Table 5. Cross-countries variation of specific mortality rate by site of infection in the IC

Auteur	Country	ICU	Years	Infected patients (n)	Mortality
Van der Kooi[19]	Germany	Surgical and medical	1997–2000	- - -	VAP: 26% UTI : 27% NB : 31%
Umscheid[20]	USA	Surgical and medical	Review	- - -	VAP: 14.4% UTI: 2.3% NB : 12.3%
Gastmeier[21]	Germany	Surgical and medical	1997–2003	8432 2759	NP : 8.9% NB : 10.9%
Appelgren[22]	Sweden	Surgical and medical	1989–1993	364	NB : 51% NP : 47% UTI : 42%
Cuellar[24]	Peru	Surgical and medical	2003–2007	- - -	VAP: 38.5% UTI: 18.5% NB: 29%
Jankovic[23]	Serbia	Surgical and medical	2010	65	VAP : 22%
Bhadade[25]	India	Surgical and medical	2002–2007	205	VAP: 56.5% UTI : 27.8% NB : 26.7%
Çağatay[26]	Turkey	Surgical	2001–2002	176	NB : 51.5%
Our study	Tunisia	Surgical and medical	2010–2011	38 10 46	NP: 38.5% UTI : 33.3% NB : 43.5%
NB: Nosocomial bacteremia; UTI: Urinary Tract Infection; NP: Nosocomial pneumonia; VAP: Ventilator associated pneumonia.					

than others. Those patients are characterized by long stay, use of mechanical ventilation, and immunosuppression.

It has been evident for decades that injuries are the leading cause of mortality in young subjects and most often without a medical history.[29] Post-traumatic infectious complications are the major cause of late mortality,[30] after neurological damages.[31] Pejorative effect of NI in patients with trauma is supported by physiological hypotheses. In fact, injuries are the leading cause of the systemic inflammatory response syndrome (SIRS).[32] SIRS is characterized by increased production of pro-inflammatory cytokines and chemokines such as Tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β, IL-6, and IL8.[33] It predisposes to multiple organ failure and immunosuppression.[34] Both increase the risk of late mortality in injured patients.

Furthermore, NB was significantly associated with mortality in the present study. Certain studies demonstrated that patients with NB have a significantly higher mortality than those without NB and for similar severity scores.[28,35] However, no association has been reported in others.[27,36] The positive association depends on NB types and causal organisms. Renaud, et al.[37] reported that mortality was significantly higher in secondary bacteremia than primary and related-catheter bacteremia. Moreover, several studies tested the effects of organisms on mortality. There is no difference in mortality between the Gram-negative bacilli resistant to antibiotics and those susceptible.[38] However, mortality was higher in infections with *Pseudomonas aeruginosa* or Methicillin resistant *Staphylococcus aureus*.[39] Finally, several studies reported similar results regarding NP,[27,28,36] UTI,[40] age,[26] gender,[21,25–27,35] SAPS-II,[21,26] infection upon admission in ICU and the prior exposure to antibiotics,[25,27,36] immunosuppression,[25,27,37] as well as use of devices.[21,22,27,28,36]

According to the World Health Organization, in low-and middle-income countries, regular monitoring of NI occurrence may be unfeasible at national level. Therefore, Ministries of Health are

unable to report information on the burden of NI.[9] In Tunisia, there is no national or regional monitoring system of NI in ICUs. Studies remain limited with different methodologies, making difficult the comparison of different rates of NI incidence and associated mortality. Therefore, we used the French protocol to collect data.

Our study has limitations. We did not include enough patients, our study was mono-centric and the results should not be generalized to other settings. We have not considered the microbiological profile of infections in the analysis of risk factors. Certainly, this profile may influence the prognosis of patients with NI. Despite limitations, our study presents strengths. The sound selection of controls is from the appropriate population at risk. This study presents the same potential sources of bias as reported in any voluntary surveillance system. Furthermore, the use of a common protocol with standard definitions of NI and the prospective data collection limit the possibility of systematic bias having affected our clinical outcomes.

Our results contribute to support other studies on NI-associated mortality in ICUs and reaffirm the importance of infection control with the involvement of all healthcare workers. They highlight the importance of establishing an active surveillance program. Surveillance activities, especially if prolonged, are the first step to identify problems and priorities, help to raise awareness of the problem and finally to decrease infection and mortality rates. Setting up a national surveillance system of NI, developing a comprehensive education program on evidence-based approaches and implementing multidisciplinary care pathways are priorities to improve the quality of care and patient safety in Tunisian ICUs.

Conflict Of Interest: *None.*
Financial Support: *None.*

References

1. Klevens RM, Edwards JR, Richards CL Jr, Horan TC, Gaynes RP, Pollock DA, et al. Estimating health care–associated infections and deaths in U.S. hospitals, 2002. *Public Health Rep*. 2007; 122: 160 – 166.
2. Allen S. Prevention and control of infection in the ICU. *Curr Anaesth Crit Care*. 2005; 16: 191 – 199.
3. Gusmão ME, Dourado I, Fiaccone R, Salvador C. Nosocomial pneumonia in the intensive care unit of a Brazilian university hospital: An analysis of the time span from admission to disease onset. *Am J Infect Control*. 2004; 32: 209 – 214.
4. Richards M, Thursky K, Buising K. Epidemiology, prevalence, and sites of infections in intensive care units. *Semin Respir Crit Care Med*. 2003; 24: 3 – 22.
5. Vincent JL, Bihari DJ, Suter PM, Bruining HA, White J, Nicolas–Chanoin MH, et al. The prevalence of nosocomial infections in intensive care units in Europe. Results of the European Prevalence of Infection in Intensive Care (EPIC) Study. EPIC International Advisory Committee. *JAMA*. 1995; 274: 639 – 644. Comment in: *JAMA*. 1996; 275: 362.
6. Chen YC, Lin SF, Liu CJ, Jiang DD, Yang PC, Chang SC. Risk factors for ICU mortality in critically ill patients. *J Formos Med Assoc*. 2001; 100: 656 – 661.
7. Shorr AF. Review of studies of the impact on Gram–negative bacterial resistance on outcomes in the intensive care unit. *Critical Care Med*. 2009; 37: 1463 – 1469.
8. Vincent JL. Nosocomial infections in adult intensive care units. *Lancet*. 2003; 361: 2068 – 2077.
9. World Health Organization. Report on the burden of endemic health care–associated infection worldwide. A systematic review of the literature. 2011. Available from: URL: http: //apps.who.int/iris/bitstream/10665/80135/1/9789241501507_eng.pdf. (Accessed Date: 5 July 2015).
10. Ministère de la santé, de la jeunesse et des sports DGS/DHOS, CTINILS–Définition des infections associées aux soins–Mai 2007. Available from: URL: http: //www.sante.gouv.fr/IMG/pdf/rapport_vcourte.pdf. (Accessed Date: 5 July 2015).
11. Institut de Veille Sanitaire, Saint Maurice–France. Réseau REA–Raisin. Surveillance des infections nosocomiales en réanimation adulte. Protocole 2009. Available from: URL: http: //www.invs.sante.fr/content/download/20606/124353/version/1/file/rea_raisin_protocole_2009.pdf. (Accessed Date: 5 July 2015).
12. Gross PA, Van Antwerpen C. Nosocomial infections and hospital deaths. A case–control study. *Am J Med*. 1983; 75: 658 – 662.
13. Schumacher M, Wangler M, Wolkewitcz M, Beyersmann J. Attributable mortality due to nosocomial infections: a simple and useful application of multistate models. *Methods Inf Med*. 2007; 46: 595 – 600.
14. Moine P, Timsit JF, De Lassence A, Troché G, Fosse JP, Alberti C, et al. Mortality associated with late – onset pneumonia in the intensive care units. *Intensive Care Med*. 2002; 28: 154 – 163.
15. Ylipalosaari P, Ala – Kokko TI, Laurila J, Ohtonen P, Syrjälä H. Intensive care acquired infection is an independent risk factor for hospital mortality: a prospective cohort study. *Crit Care*. 2006; 10: R66.
16. Januel JM, Harbarth S, Allard R, Voirin N, Lepape A, Allaouchiche B, et al. Estimating attributable mortality due to nosocomial infections acquired in intensive care units. *Infect Control Hosp Epidemiol*. 2010; 31: 388 – 394.
17. Dasgupta S, Das S, Chawan NS, Hazra A. Nosocomial infections in the intensive care unit: Incidence, risk factors, outcome and associated pathogens in a public tertiary teaching hospital of Eastern India. *Indian J Crit Care Med*. 2015; 19: 14 – 20.
18. Cevik MA, Yilmaz GR, Erdinc FS, Erdinc FS, Ucler S, Tulek NE. Relationship between nosocomial infection and mortality in a neurology intensive care unit in Turkey. *J Hosp Infect*. 2005; 59: 324 – 330.
19. van der Kooi TI, de Boer AS, Manniën J, Wille JC, Beaumont MT, Mooi BW, et al. Incidence and risk factors of device–associated infections and associated mortality at the intensive care in the Dutch surveillance system. *Intensive Care Med*. 2007; 33: 271 – 278.
20. Umscheid CA, Mitchell MD, Doshi JA, Agarwal R, Williams K, Brennan PJ. Estimating the proportion of healthcare–associated infections that are reasonably preventable and the related mortality and costs. *Infect Control Hosp Epidemiol*. 2011; 32: 101 – 114.
21. Gastmeier P, Sohr D, Geffers C, Behnke M; Rüden H. Risk Factors for Death Due to Nosocomial Infection in Intensive Care Unit Patients: Findings From the Krankenhaus Infektions Surveillance System. *Infect Control Hosp Epidemiol*. 2007; 28: 466 – 472.
22. Appelgren P, Hellstrom I, Weitzberg E, Söderlund V, Bindslev L, Ransjö U. Risk factors for nosocomial intensive care infection: a long – term prospective analysis. *Acta Anaesthesiol Scand*. 2001; 45: 710 – 719.
23. Janković SM, Djordjevic Z. Factors associated with death in intensive care unit patients having ventilator associated pneumonia. *Ser J Exp Clin Res*. 2012; 13: 131 – 137.
24. Cuellar LE, Fernandez–Maldonado E, Rosenthal VD, Castaneda–Sabogal A, Rosales R, Mayorga–Espichan MJ, et al. Device–associated infection rates and mortality in intensive care units of Peruvian hospitals: findings of the International Nosocomial Infection Control Consortium. *Pan Am J Public Health*. 2008; 24: 16 – 24.
25. Bhadade R. Prospective evaluation and mortality outcome of nosocomial infections in medical intensive care unit at tertiary care teaching centre in Mumbai. *Emergency Med*. 2013; 3: 1 – 7.
26. Cağatay AA, Ozcan PE, Gulec L, Ince N, Tugrul S, Ozsut H, et al. Risk factors for mortality of nosocomial bacteraemia in intensive care units. *Med Princ Pract*. 2007; 16: 187 – 192.
27. Myny D, Depuydt P, Colardyn F, Blot S. Ventilator–associated pneumonia in a tertiary care ICU: analysis of risk factors for acquisition and mortality. *Acta Clin Belg*. 2005; 60: 114 – 121.
28. Combes A, Luyt CE, Trouillet JL, Nieszkowska A, Chastre J. Gender impact on the outcomes of critically ill patients with nosocomial infections. *Crit Care Med*. 2009; 37: 2506 – 2511.
29. Moore FA, Moore EE. Evolving concepts in the pathogenesis of post injury multiple organ failure. *Surg Clin North Am*. 1995; 75: 257 – 277.
30. Pories SE, Gamelli RL, Mead PB, Goodwin G, Harris F, Vacek P. The epidemiologic features of nosocomial infections in patients with trauma. *Arch Surg*. 1991; 126: 97 – 99.
31. Morgan AS. Risk factors for infection in the trauma patient. *J Natl Med Assoc*. 1992; 84: 1019 – 1023.
32. Sherwood E, Koutrouvelis A. *Trauma–induced immunosuppression:*

Pathogenesis and Treatment. In: Vincent J, editor. Yearbook of Intensive Care and Emergency Medicine Berlin: Springer–Verlag; 2000: 51 – 62.
33. Faist E, Kim C. Therapeutic immunomodulatory approaches for the control of systemic inflammatory response syndrome and the prevention of sepsis. *New Horiz*. 1998; 6: 97 – 102.
34. Édouard A, Tadié JM, Asehnoune K, Moine P. Particularités des polytraumatisés à l'égard des infections nosocomiales Nosocomial infections in trauma patients. *Réanimation*. 2003; 12: 227 – 234. [Article in French]
35. Prowle JR, Echeverri JE, Ligabo EV, Sherry N, Taori GC, Crozier TM, et al. Acquired bloodstream infection in the intensive care unit: incidence and attributable mortality. *Crit Care*. 2011; 15: R100. doi: 10.1186/cc10114
36. Kallel H, Dammak H, Bahloul M, Ksibi H, Chelly H, Ben Hamida C, et al. Risk factors and outcomes of intensive care unit–acquired infections in a Tunisian ICU. *Med Sci Monit*. 2010; 16: 69 – 75.
37. Renaud B, Brun–Buisson C, ICU–Bacteremia Study Group. Outcomes of primary and catheter – related bacteremia. A cohort and case – control study in critically ill patients. *Am J Respir Crit Care Med*. 2001; 163: 1584 – 1590.
38. Blot S, Vandewoude KH, Colardyn FA. Clinical impact of nosocomial Klebsiella bacteremia in critically ill patients. *Eur J Clin Microbiol Infect Dis*. 2002; 21: 471 – 473.
39. Osmon S, Warren D, Seiler SM, Shannon W, Fraser VJ, Kollef MH. The influence of infection on hospital mortality for patients requiring > 48 h of intensive care. *Chest*. 2003; 124: 1021 – 1029.
40. Laupland KB, Zygun DA, Davies HD, Church DL, Louie TJ, Doig CJ. Incidence and risk factors for acquiring nosocomial urinary tract infection in the critically ill. *J Crit Care*. 2002; 17: 50 – 57.