Infectious disease

Risk factors for carbapenem-resistant *Klebsiella pneumoniae* infections in Intensive Care Units: a multicentre case-control study with a competing-risks analysis

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Keywords

Klebsiella pneumoniae • Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) infections • Intensive Care Units • Risk factors

Summary

Aim. *This study investigated the risk factors for the development of carbapenem-resistant Klebsiella pneumoniae (CRKP) infections in adult patients in Intensive Care Units (ICUs).*
Methods. *A multicentre case-control study was conducted in ICUs in three tertiary hospitals in Turkey. The cases were patients culture-confirmed CRKP and a condition associated with healthcare-associated infections. Two controls were randomly selected for each case from among all other patients with an ICU stay at least as long as that of the corresponding case-patient. A proportional semiparametric subdistribution hazards regression model was used to assess risk factors for CRKP infection. ICU discharge and non-CRKP-related deaths were treated as competing risks.*
Results. *A total of 120 patients, 44 cases and 76 controls were included in the analysis. Of the controls, 32 were discharged from the ICU and 44 died without acquiring CRKP infection. Endotracheal intubation (hazard ratio [HR]: 1.96, 95% confidence interval [CI]: 1.00-3.868) and type 2 diabetes mellitus (HR: 1.57, 95% CI: 0.888-2.806) were associated with an increased risk of CRKP infection, whereas carbapenem exposure (HR: 0.47, 95% CI: 0.190-1.1175) and the presence of a nasogastric tube (HR: 0.49, 95% CI: 0.277-0.884) were associated with a decreased risk of CRKP infection.*
Conclusions. *Enteral nutrition support via a nasogastric tube may be associated with a reduced risk of CRKP-resistant infections in ICU patients. This hypothesis should be tested with a well-designed study.*

Introduction

Klebsiella pneumoniae causes lung, urinary tract, and bloodstream infections, especially in the older and immunosuppressed patients [1]. Urinary, endotracheal, venous (especially femoral vein), nasogastric, and other feeding catheters are risk factors that may cause infection by mucosal colonisation [2, 3]. *K. pneumoniae* has transcriptomic activity that is associated with enhanced colonisation, virulence, and antibiotic resistance through genomic loci located on chromosomes and plasmids [4]. These genetic activities are thought to be expressed in the presence of inducing factors, especially antibiotics [5].
Intensive Care Units (ICUs) are a high-risk setting for carbapenem-resistant *K. pneumoniae* (CRKP) infections because of the presence of vulnerable hosts, an abundance of invasive procedures, and polypharmacy. CRKP infections have high morbidity and mortality rates [6]. The limited availability of the new beta-lactam and beta-lactamase inhibitor combinations (such as ceftazidime-avibactam) makes treatment of infection challenging, particularly in limited-resource settings.
Determining individual risk factors for CRKP infections is important for early diagnosis and treatment [7]. Screening for carbapenem-resistant *Enterobacterales* (CRE), vancomycin-resistant enterococcus (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA) is a standard ICU admission procedure in tertiary hospitals in Turkey.
Studies to determine risk factors are generally carried out with a case-control design. Previous case-control studies of risk factors for CRKP infection have had several limitations in terms of study design and statistical methods [8, 9]. In this study, we aimed to determine the risk factors for the development of CRKP infections in adult ICU patients using a proportional semiparametric subdistribution hazards regression model to overcome the biases of previous studies.

Methods

Study design, settings, and patient selection

We conducted this case-control study at three tertiary hospitals in Turkey. A Microsoft Access database was created and distributed it to the participating centres. To ensure data validity, data input was restricted by dropdown lists to the names of drugs (supplied by the World Health Organization), names of microorganisms, and underlying diseases. Subjects were selected patients who admitted to ICU units between January 2017 and December 2019.This study was approved by the Ethical Committee of Istanbul Medeniyet University. The requirement for informed consent was waived because of its retrospective design.

The inclusion criteria for the study were defined as follows: patients aged 18 and older, who stayed in the intensive care unit for at least three days, and had CRKP growth in at least one culture during their intensive care admission. Pregnant individuals and patients under the age of 18 were not included in the study. Patients who had CRKP colonisation or CRKP infection diagnosed before the third day of ICU admission were excluded from the study because it was not possible to rule out pre-ICU factors as the source of the CRKP infection.

Antimicrobial susceptibility test

Bacteraemia was defined as the isolation of *K. pneumoniae* in a blood culture. Bacterial identification and routine antimicrobial susceptibility testing were performed. We processed all cultures with ready-to-use media, identified bacteria using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry MALDI-TOF MS (VITEK MS, bioMérieux, France), and performed antimicrobial susceptibility tests usingVITEK-2 (bioMérieux) according to Clinical and Laboratory Standards Institute recommendations. CRKP was defined according to the European Committee on Antimicrobial Susceptibility Testing definition as an isolate with an ertapenem minimal inhibitory concentration (MIC) ≥ 2 μg/mL), or imipenem and/or meropenem MIC ≥ 4 μg/mL. The *K. pneumoniae* isolates susceptible to ertapenem, imipenem, and meropenem were considered as CSKP. We performed antimicrobial susceptibility tests for *K. pneumoniae* isolates using VITEK-2 and confirmed carbapenem resistance of isolates using ertapenem E-test (bioMérieux). We determined the MICs of ceftazidime, ceftazidime-avibactam, meropenem, meropenem-sulbactam, and colistin using microdilution tests.

Definitions

Cases were patients who had a positive microbiological culture for CRKP and a condition associated with healthcare-related infections. The consulting infectious disease physician notes were extracted and recorded to ensure that this condition was met. For each patient case, two control patients were randomly chosen from all other ICU patients who had spent at least the same "time at risk" as the corresponding case-patient. In this context, "time at risk" refers to the duration between ICU admission and either the occurrence of an event or the time of censoring. For cases, event time was the time when the first CRKP infection was detected. For patients who died or were discharged without being diagnosed with CRKP infection, time at risk was defined as the time between admission and death or discharge, respectively. Prior exposure to a drug was defined as a drug being used for more than one day and started at least three days prior to the event time. For controls, prior exposure to the drug was present if the drug was used for at least three days before discharge or death, as applicable.

A total of 12 variables were found suitable for potentially predictive and were considered in the variable selection procedure: centre; age; sex; carbapenem (mostly meropenem, imipenem and ertapenem) use; 3^{rd}-/4^{th}-generation cephalosporin (ceftriaxone,ceftazidime, cefepime) use; and piperacillin/tazobactam (only) use; central venous catheter; haemodialysis catheter; intubation tube; thorax tube (for chest drain); tracheostomy tube; and nasogastric tube insertions. All patients had urinary catheters. Type 2 diabetes mellitus (T2DM) was included as an underlying disease.

Statistical analysis

Descriptive values were computed as means, standard deviations, medians and count/percent frequencies, depending on the variable type. The data did not include missing observations and had a right-censored (discharge from ICU) competing risk design with two failure events. ICU-acquired CRKP infection was the failure event of interest. A number of patients died (competing risk) before acquiring CRKP. Therefore, death was the second failure event that prevented the occurrence of the primary event. To estimate the effects of covariates on the failure event (CRE infection) in competing risk data, the proportional semiparametric subdistribution hazards model, which is a slight modification of the Fine and Gray approach to account for between-centre heterogeneity in multicentre studies, was used [10]. This model directly compares the cumulative incidence function by modelling the so-called hazard of the subdistribution. The cumulative incidence is the probability of failure for a particular cause in the presence of other causes. In the first stage of modelling, the full model was established.

With the backward variable selection and purposeful variable selection methods, variables included in the full model which have a statistically significant ($p \leq 0.05$) effect on infection risk, and variables considered to be clinically important or significant (that is, $0.05 < p < 0.15$) were included in the model, and the final model was obtained. Because the differences between centres were not statistically significant, centre was excluded from the model. Stata version 14 (StataCorp LP, College Station, TX, USA) was used for data analysis.

Tab. I. Demographics, baseline and outcome characteristics of the study population.

	CRKP infection		
Variables	No[1] N = 76	Yes N = 44	p
Gender[£]			0.666
Male	37 (49%)	24 (54,5%)	
Female	39 (51%)	20 (55,5%)	
Age[¥]	68.2 ± 19.0	71.4 ± 15.9	0.354
Time under the risk[§]	17 [9-24]	17 [10-27]	0.434
APACHE II score	21 [17-28]	21 [15-28]	0.852
SOFA score	6 [4-9]	7 [4-9]	0.366
VAP	-	14 (30%)	
Bacteremia	-	27 (49%)	
Urinary tract infection	-	1 (2%)	
Soft tissue infection	-	2 (4, 5%)	
Diabetes mellitus	15 (19.7%)	16 (36.4%)	**0.045**
Outcome			0.670
Discharged	44 (58%)	16 (36%)	
Died	32 (42%)	28 (64%)	

[¥] Mean ± SD for normal distributed variables. [§] Median [25th-75th] for other distributed variables. [£] n (%). [1] Discharged or died before CRKP occurred. Competing = 44, Cencoring = 32.

Results

ICU records of a total of 285 patients were obtained. Of these patients, 54 had CRKP growth on culture. Nine cases were excluded from the study because CRKP growth on a sample collected on the first day of hospitalisation. One 5-year-old boy was excluded because the study was restricted to patients aged ≥18 years. Eight patients could not be included in the control group because their hospital records were incomplete. Therefore, data from 44 cases and 76 controls (a total of 120 patients) were used in the analysis. Of the controls, 32 were discharged from the ICU and 44 died without CRKP infection. Patient demographics, baseline characteristics, and outcomes are presented in Table I.

The full model results in which all risk factors are included in the model are given in Table II. The final model selected after using the combined backward variable elimination and purposeful variable selection method is given in Table III.

The final model revealed that endotracheal intubation and the presence of T2DM were associated with an increased CRKP infection risk, whereas carbapenem exposure and a nasogastric tube insertion were associated with a decreased risk of CRKP infection. The cumulative incidence according to each of the four significant risk factors is given in Figures 1-4.

Discussion

Patients with a nasogastric tube had a significantly lower risk of CRKP infection. This suggests that continuity of enteral nutrition may be an important factor in preventing CRKP infections in ICU patients. Contrary to

Tab. II. Results of full proportional semiparametric subdistribution hazards model.

	sHR[(i)]	95% CIs		
		ll[(ii)]	ul	p-value
Centers				
2	**1.24**	0.275	5.60	0.777
3	0.723	0.160	3.26	0.673
Gender	1.183	0.648	2.15	0.583
TZP exposure	0.708	0.234	**2.14**	0.542
Cephalosporin exposure	1.014	0.98	1.03	0.63
Carbapenem exposure	0.387	0.116	1.28	0.120
Haemodialysis catheter	1.045	0.495	2.18	0.915
Nasogastric_tube	0.380	0.188	0.768	**0.007**
Endotracheal_intubation	3.355	1.315	8.561	**0.011**
Thorax tube	0.752	0.370	1.529	0.432
Tracheostomy	1.525	0.796	2.932	0.202
Diabetes mellitus	0.995	0.978	1.013	0.652

[(i)] sHR, subdistribution Hazard Ratio for CRKP infection. [(ii)] ll & ul, lower and upper limits of confidence interval.

Tab. III. Results of final proportionalsemiparametric subdistribution hazards model.

	sHR[(iii)]	95% CIs		
		ll[(iii)]	ul	p-value
Carbapenem exposure	0.47	0.190	1.175	0.107
Nasogastric tube	0.49	0.277	0.884	0.018
Endotracheal intubation	1.96	1.00	3.868	0.050
Diabetes mellitus	1.57	0.888	2.806	0.120

[(iii)] sHR, subdistribution Hazard Ratio for CRKP infections. [(iii)] ll & ul, lower and upper limits of confidence interval.

Fig. 1. Cumulative incidence by exposure to carbapenem.

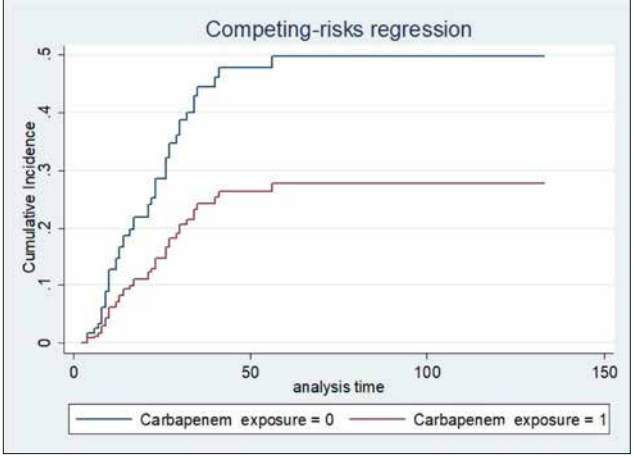


Fig. 2. Cumulative incidence in nasogastric tube use.

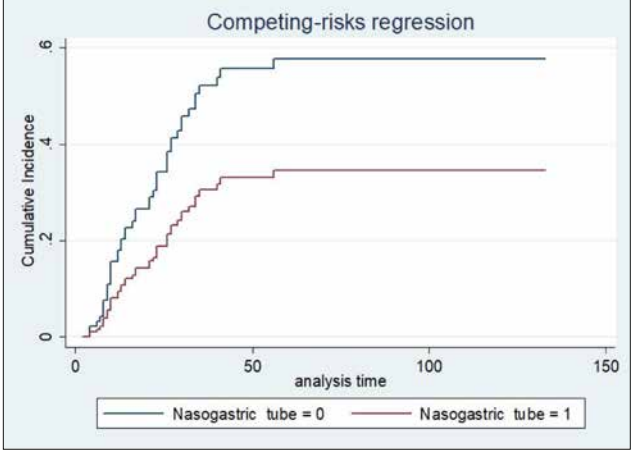


Fig. 3. Cumulative incidence in endotracheal intubation.

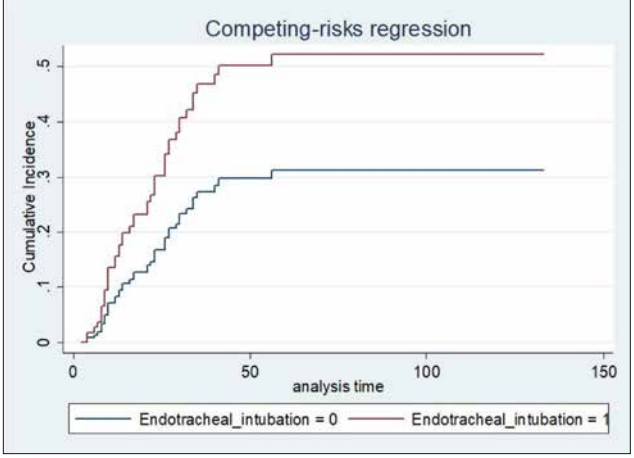
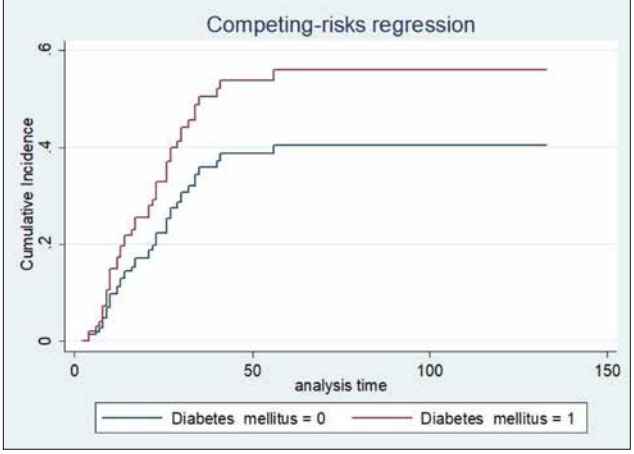


Fig. 4. Cumulative incidence in the presence of diabetes mellitus.



previous studies, carbapenem exposure was associated with a decreased risk, rather than an increased risk, of CRKP infection [11, 12]. We found that T2DM and endotracheal intubation were underlying risk factors for CRKP infection in ICU patients.

The use of broad-spectrum antibiotics results in increased colonisation by drug-resistant pathogens. In a large prospective intensive care surveillance study, CRKP colonisation did not increase during the hospitalisation period in individuals with prior carbapenem exposure, but increased significantly in cultures taken one month after hospitalisation [13]. This illustrates that not every colonisation turns into infection. Our study evaluated factors that facilitate the transition from colonisation to infection, and the time taken for this process to occur. Our study differs from other studies due to the parametric analysis of the use of catheters that bypass natural immunity and the use of a cumulative hazard time-to-infection approach. Many previous studies have revealed a linear relationship between antibiotic pressure and antibiotic resistance. Our study and other studies obtained different results that may be related to the cause of diversity of resistance mechanisms.

In ICUs, nasogastric tube-mediated nutrition keeps the intestinal tract relatively functional and provides the continuity of the commensal relationship between mucosal immunity and intestinal flora [14]. The results of one of our previous studies on risk factors for invasive candidaemia in ICU patients emphasised the importance of gut functionality and integrity with regard to infection prevention [15]. In this study, we have found prior exposure to N-acetylcysteine that might have an independent role in the health of enterocytes.

High quality enteral nutrition in ICU patients can reduce the risk of developing serious infections and the risk of death [16]. A prospective observational study showed that greater amounts of energy and protein intake were associated with lower infection rate, especially when given more than 96 h after admission [17].

On contrary, when parenteral nutrition is added to support standard enteral nutrition, the risk of intra-abdominal and catheter-related infections increases [18]. There is, however, a lack of consensus on the risks and benefits of parenteral versus standard enteral nutrition in ICU patients, and a meta-analysis on this subject was

inconclusive because of the heterogeneity of the studies and various biases in the included studies [19].
Our study has some limitations. Its main weaknesses are its retrospective nature and the limited sample size. Other underlying diseases that may increase the risk of infection in intensive care patients (cirrhosis, haematologic or solid organ tumours, transplantation) were not included in the analysis because of the limited sample size and their even distribution in the case and control groups.

Conclusions

To our knowledge, this study is the first case-control study with a competing risks analysis of risk factors for CRKP infection in ICU patients. The routine performance of blood culture of patients on admission to the ICU patients with CRKP colonisation to be excluded from the case group.
In conclusion, provision of enteral nutrition support may help to reduce the incidence of CRKP infection in ICU patients. This hypothesis should be tested with well-designed studies.

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Conflict of interest statement

The authors declare that they have no competing interests.

Authors' contributions

FA and HV made concept, designed and wrote the study. HA did statistical analysis and interpreted the results. Selection of patients and control group and acquisition of data were proved by EA, SS, HCD, AÖ, SA, HOE, AM. All authors read and approved the final manuscript.

References

[1] Frontiers | Colonization, Infection, and the Accessory Genome of Klebsiella pneumoniae | Cellular and Infection Microbiology. https://www.frontiersin.org/articles/10.3389/fcimb.2018.00004/full (Accessed on: 9/1/2021).

[2] Zheng X, Wang J, Xu W, Xu J, Hu J. Clinical and molecular characteristics, risk factors and outcomes of Carbapenem-resistant Klebsiella pneumoniae bloodstream infections in the intensive care unit. Antimicrob Resist Infect Control 2017;6:102. https://doi.org/10.1186/s13756-017-0256-2

[3] Humphries RM, Yang S, Kim S, Muthusamy VR, Russell D, Trout AM, Zaroda T, Cheng QJ, Aldrovandi G, Uslan DZ, Hemarajata P, Rubin ZA. Duodenoscope-Related Outbreak of a Carbapenem-Resistant Klebsiella pneumoniae Identified Using Advanced Molecular Diagnostics. Clin Infect Dis 2017;65:1159-66. https://doi.org/10.1093/cid/cix527

[4] Holt KE, Wertheim H, Zadoks RN, Baker S, Whitehouse CA, Dance D, Jenney A, Connor TR, Hsu LY, Severin J, Brisse S, Cao H, Wilksch J, Gorrie C, Schultz MB, Edwards DJ, Nguyen KV, Nguyen TV, Dao TT, Mensink M, Minh VL, Nhu NTK, Schultsz C, Kuntaman K, Newton PN, Moore CE, Strugnell RA, Thomson NR. Genomic analysis of diversity, population structure, virulence, and antimicrobial resistance in Klebsiella pneumoniae, an urgent threat to public health. Proc Natl Acad Sci 2015;112:E3574-81. https://doi.org/10.1073/pnas.1501049112

[5] Paczosa MK, Mecsas J. Klebsiella pneumoniae: going on the offense with a strong defense. Microbiol Mol Biol Rev 2016;80:629-61. https://doi.org/10.1128/MMBR.00078-15

[6] Xu L, Sun X, Ma X. Systematic review and meta-analysis of mortality of patients infected with carbapenem-resistant Klebsiella pneumoniae. Ann Clin Microbiol Antimicrob 2017;16:18. https://doi.org/10.1186/s12941-017-0191-3

[7] Shields RK, Nguyen MH, Chen L, Press EG, Potoski BA, Marini RV, Doi Y, Kreiswirth BN, Clancy CJ. Ceftazidime-Avibactam Is Superior to Other Treatment Regimens against Carbapenem-Resistant Klebsiella pneumoniae Bacteremia. Antimicrob Agents Chemother 2017;61:e00883-17. https://doi.org/10.1128/AAC.00883-17

[8] Evans SR, Harris AD. Methods and issues in studies of CRE. Virulence 2017;8:453-9. https://doi.org/10.1080/21505594.2016.1213473

[9] Tsioutis C, Eichel VM, Mutters NT. Transmission of Klebsiella pneumoniae carbapenemase (KPC)-producing Klebsiella pneumoniae: the role of infection control. J Antimicrob Chemother 2021;76:i4-i11. https://doi.org/10.1093/jac/dkaa492

[10] Zhou B, Latouche A, Rocha V, Fine J. Competing risks regression for stratified data. Biometrics 2011;67:661-70. https://doi.org/10.1111/j.1541-0420.2010.01493.x

[11] Marimuthu K, Ng OT, Cherng BPZ, Fong RKC, Pada SK, De PP, Ooi ST, Smitasin N, Thoon KC, Krishnan PU, Ang MLT, Chan DSG, Kwa ALH, Deepak RN, Chan YK, Chan YFZ, Huan X, Zaw Linn K, Tee NWS, Tan TY, Koh TH, Lin RTP, Hsu LY, Sengupta S, Paterson DL, Perencevich E, Harbarth S, Teo J, Venkatachalam I, CaPES Study Group. Antecedent Carbapenem Exposure as a Risk Factor for Non-Carbapenemase-Producing Carbapenem-Resistant Enterobacteriaceae and Carbapenemase-Producing Enterobacteriaceae. Antimicrob Agents Chemother 2019;63:e00845-19. https://doi.org/10.1128/AAC.00845-19

[12] Liu P, Li X, Luo M, Xu X, Su K, Chen S, Qing Y, Li Y, Qiu J. Risk factors for carbapenem-resistant Klebsiella pneumoniae infection: a meta-analysis. Microb Drug Resist Larchmt N 2018;24:190-8. https://doi.org/10.1089/mdr.2017.0061

[13] Ruiz J, Gordon M, Villarreal E, Frasquet J, Sánchez MÁ, Martín M, Castellanos Á, Ramirez P. Influence of antibiotic pressure on multi-drug resistant Klebsiella pneumoniae colonisation in critically ill patients. Antimicrob Resist Infect Control 2019;8:38. https://doi.org/10.1186/s13756-019-0484-8

[14] Kreymann KG, Berger MM, Deutz NEP, Hiesmayr M, Jolliet P, Kazandjiev G, Nitenberg G, van den Berghe G, Wernerman J, Ebner C, Hartl W, Heymann C, Spies C. ESPEN guidelines on enteral nutrition: intensive care. Clin Nutr 2006;25:210-23. https://doi.org/10.1016/j.clnu.2006.01.021

[15] Arslan F, Caskurlu H, Sarı S, Dal HC, Turan S, Sengel BE, Gul F, Yesilbag Z, Eren G, Temel S, Alp E, Gol Serin B, Kose S, Calık S, Tuncel ZT, Senbayrak S, Sarı A, Karagoz G, Tomruk SG, Sen

B, Hizarci B, Vahaboglu H. Risk factors for noncatheter-related Candida bloodstream infections in Intensive Care Units: a multicenter case-control study. Med Mycol 2019;57:668-74. https://doi.org/10.1093/mmy/myy127

[16] Immune enhancing enteral nutrition reduced mortality and acquired infections in intensive care unit patients with sepsis. Evid Based Nurs 2000;3:120. https://doi.org/10.1136/ebn.3.4.120

[17] Heyland DK, Stephens KE, Day AG, McClave SA. The success of enteral nutrition and ICU-acquired infections: a multicenter observational study. Clin Nutr Edinb Scotl 2011;30:148-55. https://doi.org/10.1016/j.clnu.2010.09.011

[18] Wischmeyer PE, Hasselmann M, Kummerlen C, Kozar R, Kutsogiannis DJ, Karvellas CJ, Besecker B, Evans DK, Preiser J-C, Gramlich L, Jeejeebhoy K, Dhaliwal R, Jiang X, Day AG, Heyland DK. A randomized trial of supplemental parenteral nutrition in underweight and overweight critically ill patients: the TOP-UP pilot trial. Crit Care Lond Engl 2017;21:142. https://doi.org/10.1186/s13054-017-1736-8

[19] Lewis SR, Schofield-Robinson OJ, Alderson P, Smith AF. Enteral versus parenteral nutrition and enteral versus a combination of enteral and parenteral nutrition for adults in the intensive care unit. Cochrane Database Syst Rev 2018;6:CD012276. https://doi.org/10.1002/14651858.CD012276.pub2

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