Prevention and treatment of ventilator-associated pneumonia: evaluation of the effectiveness of a prevention bundle and ceftolozane/tazobactam therapy

PhD thesis

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Budapest
2023

1. INTRODUCTION

Ventilator-associated pneumonia (VAP) and the consecutive sepsis are widely recognized as detrimental and possibly lethal complications of the critically ill. In the past decades, incidence of VAP remained high despite prevention efforts. Care bundles combining multiple prevention measures were shown to be effective in lowering VAP rates. However, the optimal bundle set is uncertain. Hand hygiene is a common component of VAP prevention bundles. There is a growing body of knowledge on care bundle implementation in the acute care setting, although a recent review was unable to identify the most effective mechanisms to integrate practices.

The development of VAP results in increased antibiotic prescription and thereby drives the spread of antimicrobial resistance. Indeed, a large proportion of VAP are caused by multidrug-resistant (MDR) and extensively drug-resistant (XDR) pathogens. Antimicrobial resistance is identified by international organizations as one of top-3 health threats requiring immediate medical countermeasures. To address this issue, novel

antimicrobials like ceftolozane/tazobactam (C/T) were developed. More reports of efficacy and safety are needed to better define the risk-benefit profile of C/T.

Greater efforts and research need to be directed towards effective prevention and treatment of VAP.

2. OBJECTIVES

- The aim of our work was to evaluate the effectiveness of a care bundle on the incidence, risk and pathogen spectrum of VAP, and on nurses' compliance to prevention measures.
- This work calls into question the long-term knowledge retention after a single educational intervention.
- We aimed to investigate both the hand disinfection technique and the compliance to hand hygiene among different groups of ICU healthcare providers.
- Regarding the therapy of VAP, we aimed to compare the efficacy and safety of ceftolozane/tazobactam and colistin in the

treatment of VAP due to XDR *Pseudomonas aeruginosa*. We aimed to identify the predictors of clinical success of antimicrobial therapy.

3. METHODS

To complete our objectives, we conducted observational studies at the Department of Anaesthesiology and Intensive Therapy, Semmelweis University.

3.1. Diagnostic criteria of ventilator-associated pneumonia

Cases of VAP were identified in patients exposed to invasive mechanical ventilation for at least 48 hours according to the presence of new lung infiltrate plus clinical evidence that the infiltrate is of an infectious origin, which include the new onset of fever, purulent sputum, leukocytosis, decline in oxygenation and positive lower respiratory tract microbiologocal sample.

VAP incidence density was calculated as follows: (total number of VAP episodes/ total amount of days of mechanical ventilation) * 1000.

3.2. Prevention program

The main strategies used to implement the care bundle were: education, development of stakeholder interrelationship and evaluation of compliance by audit. Components of the care bundle are shown in Table 1. The educational meetings were initiated in July 2015 for the first time, and in June 2020 for the second time.

Table 1. Components of the care bundle

Prevention measure	Detailed description
Hand hygiene	Indicated according to the 5 moments of hand hygiene
Oral care	0,12% chlorhexidine Every 12 hours
Cuff pressure control	20-25 cmH_2O Every 12 hours
Head-of-bed elevation	30-45º position in the daytime anti-Trendelenburg position in the night
Aseptic endotracheal suction and circuit manipulation	Sterile gloves and suction catheter Remove condensate from circuit

3.3. Compliance assessment

Hand hygiene, aseptic ventilator circuit manipulation and head-of-bed elevation was assessed by direct observations as the gold standard. Compliance rates for these measures were calculated as the number of episodes where the recommendations were correctly applied and divided by the number of opportunities to do so. Data regarding oral care and intermittent cuff pressure control were obtained

by review of daily nursing administration sheets. Compliance was defined as at least one documented cuff pressure assessment and oral care within the bundle recommendation during one shift observation. Compliance was measured in the pre-implementation and post-implementation phases during 2015, and was measured before the bundle implementation, then 3 months and 12 months thereafter during 2020 and 2021.

3.4. Hand hygiene technique assessment

Data regarding hand hygiene technique were collected by using the Semmelweis Scanner technology (Semmelweis Scanner, HandInScan Ltd., Debrecen). The device detects the disinfectant's coverage on both sides of the hands based on image analysis and produces real-time, visual and numerical feedback. Proper hand hygiene technique was considered as at least 95% coverage of the hands.

3.5. Statisztikai megfontolások

Continuous variables showing normal distribution were reported as means +/- standard deviations (SD) and were compared by Student's t-test. Non-normal data were reported as medians and interquartile ranges (IQR) and

were compared by Mann-Whitney U test, Kruskal-Wallis test and by Dunn's post hoc test. The Chi square test or Fisher's exact test was used to compare categorical variables. A p-value ≤ 0.05 was considered as statistically significant.

4. RESULTS

4.1. The importance of education of ICU nurses on ventilator-associated pneumonia prevention

4.1.1. Compliance to preventive measures

Two hundred and seventy-five patients were enrolled in the pre-implementation period from January 2015 to June 2015, and 260 of them were enrolled in the post-implementation period from July 2015 to December 2015. Figure 1 shows the change of compliance for individual elements of the prevention bundle after education. Improved compliance was achieved regarding head-of-bed elevation, oral care, hand hygiene, endotracheal suctioning in sterile gloves, and condensate removing from ventilator circuit.

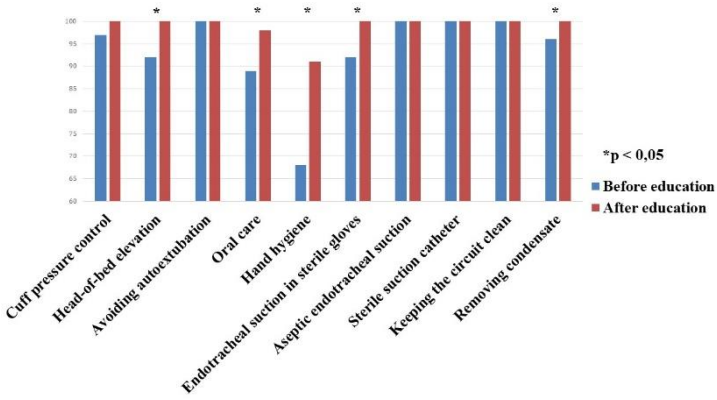


Fig. 1.
Compliance to prevention measures in the pre- and post-implementation period. χ^2 test.

4.1.2. Epidemiology of ventilator-associated pneumonia

During the pre-implementation period, the incidence density of VAP was 21,5/1000 ventilator-days (95% CI 14,17-31,10), which decreased to 12,0/1000 ventilator-days (95% CI 7,2-19,49). The relative risk reduction was 44% (95% CI -0,4-0,97).

4.1.3. Microbiology of ventilator-associated pneumonia

Ventilator-associated pneumonia due to *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Stenotrophomonas*

maltophilia decreased, while VAP due to *Acinetobacter baumannii* increased in the post-implementation period. *Enterobacterales* bacteria were isolated in 6 cases before education, while *Klebsiella oxytoca* and *Klebsiella pneumoniae* were isolated in 3 cases after education.

4.2. The long-term compliance to preventive measures

4.2.1. Change of compliance to preventive measures

Compliance to each preventive measure improved at 3 months after bundle implementation. Compliance with head-of-bed elevation remained high throughout the study period (91 % after three months and 92 % after 12 months of bundle implementation). On the other hand, compliance with the four other bundle elements decreased to their baseline levels after 12 months. Change of compliance over time for the preventive measures is shown in Figure 2.

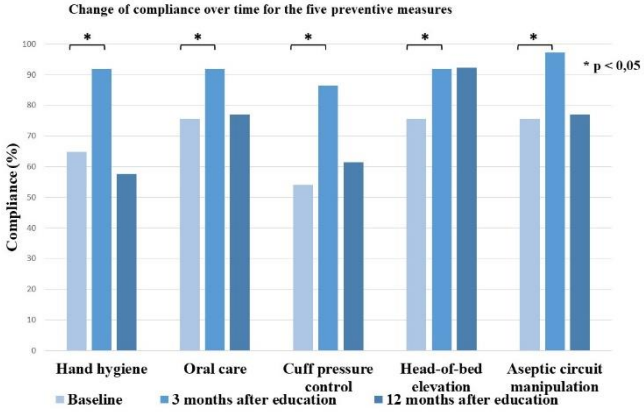


Fig. 2.
Change of compliance over time for the five prevention measures. χ^2 test.

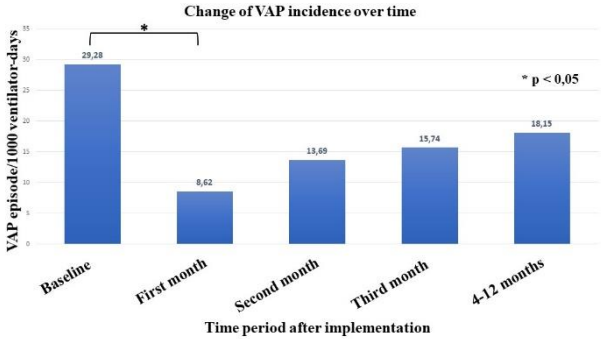


Fig. 3.
Change of VAP incidence over time. χ^2 test.

Table 2. Hazard ratio of variables associated with occurrence of ventilator-associated pneumonia in the Cox proportional hazard model.

APACHE II = Acute Physiology And Chronic Health Evaluation II; CI = confidence interval; HR = hazard ratio; IRRT = intermittent renal replacement therapy; CRRT = continuous renal replacement therapy

* p < 0,05

	Univariate analysis			Multivariate analysis		
Variable	**HR**	**95% CI**	**p**	**HR**	**95% CI**	**p**
Age	0,99	0,98-1,00	0,44	-	-	-
Male sex	1,78	1,04-3,03	0,03*	1,88	1,09-3,22	0,02*
APACHE II	1,01	0,98-1,04	0,28	1,01	0,98-1,04	0,35
IRRT	1,45	0,81-2,61	0,20	-	-	-
CRRT	1,54	0,81-2,61	0,17	-	-	-
Peripheral arterial disease	0,78	0,46-1,32	0,36	-	-	-
Liver disease	0,49	0,17-1,36	0,17	-	-	-
Diabetes mellitus	1,15	0,67-1,95	0,60	-	-	-
Other immunosuppressive therapy	1,11	0,56-2,19	0,75	-	-	-
Post-implementation period	0,41	0,24-0,70	<0,01*	0,41	0,24-0,71	<0,01*

4.2.2. Incidence and risk of ventilator-associated pneumonia

In the first month after the educational intervention, the incidence density of VAP decreased from 29,3 to 8,62/1000 ventilator-days (p = 0,03). VAP incidence

increased to 18,15/1000 ventilator-days during the four to 12-month after the implementation period (Figure 3).

The care bundle decreased VAP incidence by 59%, whereas male sex was associated with a significantly higher occurence of VAP (Table 2.)

4.3. Implementation of immediate feedback system into hand hygiene practice in the ICU

4.3.1. Hand disinfection technique

The Semmelweis Scanner device recorded 604 measurements. Results are shown in Table 3 and Figure 4.

4.3.2. Compliance to hand hygiene

A total of 162 direct observations were performed and an average 60,49% hand hygiene compliance was calculated (Table 4.). The comparative analysis between the doctor and nurse group revealed insignificant difference in hand hygiene compliance (p = 0,26).

Table 3. Hand disinfection results in groups of the ICU staff.

ICU staff	Number of measurements		Pass rate (%)
	Pass (n)	Fail (n)	
Doctor	24	8	75,0%
Nurse	318	49	86,6%
Nursing assistant	120	21	85,1%
Head-nurse	5	0	100%
Surveillance nurse	7	1	87,5%
Physiotherapist	49	2	96,0%
Total	523	81	86,5%

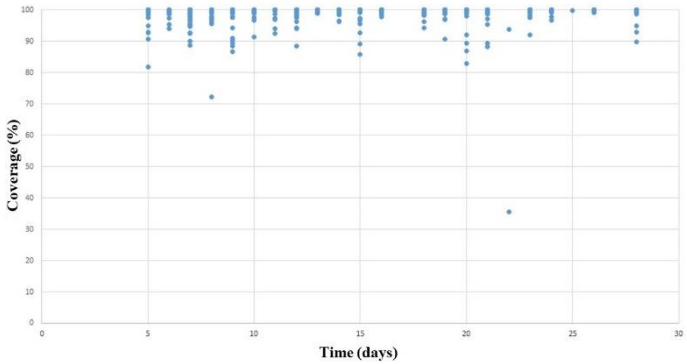
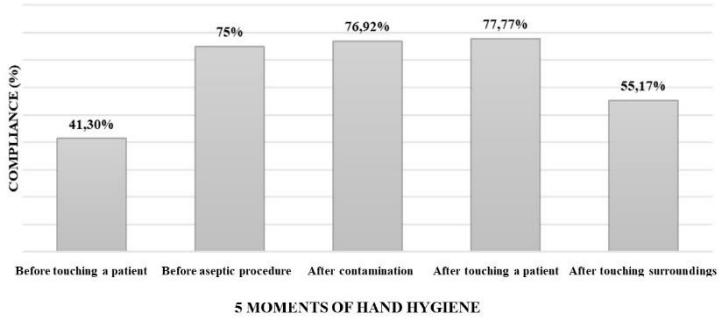


Fig. 4.
Scatterplot of disinfectant coverage.

Table 4. Hand hygiene compliance rate in groups of the ICU staff.

ICU staff	Number of measurements		Compliance (%)
	Pass (n)	Fail (n)	
Doctor	34	29	53,97%
Nurse	56	33	62,92%
Nursing assistant	4	0	100%
Physiotherapist	4	2	66,66%
Total	98	64	60,49%

Compliance was evaluated according to the „5 moments" concept. Figure 5 shows the results based on 192 observations. Low compliance was observed before touching the patient (41,30%), and after touching patient surroundings (55,17%).



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A direkt obszerváció eredményei a kézhigiéne 5 momentuma alapján.

4.4. Ceftolozane/tazobactam versus colistin in the treatment of VAP due to XDR *Pseudomonas aeruginosa*

4.4.1. Patient and treatment characteristics

A total of 51 patients were available for analysis. Eighteen patients were assigned to the ceftolozane/tazobactam (C/T) group and 33 to the colistin (CMS) group. Baseline conditions in terms of demographics, severity of acute illness and comorbidities were similar in the two groups without any statistically signifcant difference.

Combination therapy was more frequently used in the CMS group (97% vs 44,4%, p=0,001) and it consisted of

inhaled colistin and systemic beta-lactams (carbapenems and piperacillin/tazobactam). Tirty-two of 33 patients in the CMS group received inhaled colistin in addition to systemic CMS; 3 of them received additional piperacillin/tazobactam and 6 of them were treated with additional carbapenems. In patients who received C/T, the additional antimicrobial agent consisted of inhaled colistin in 6 cases and a systemic beta-lactam in 2 cases. Additional systemic antimicrobial agents were inefective against the XDR pathogen in all cases. Among patients who received C/T, 9 were given a 1,5 g base dose and 9 received a 3 g base dose (or the renal adjusted dose).

4.4.2. Outcome

Clinical success was demonstrated in 13 C/T patients (72,2%) compared with 10 patients (30,3%) who received CMS (OR 5,98, 95% CI 1,67–21,31, p=0,007). Clinical success rate did not differ in those who received the standard (66,7%, n=6) or high (77,8%, n=7) dose of C/T (p=0,50).

In multivariate logistic regression analysis we included age, Charlson Comorbidity Index, APACHE II score,

polymicrobial infection and continuous renal replacement therapy as potential factors associated with clinical success rate. Ceftolozane/tazobactam antibiotic therapy was verifed to be an independent predictor for clinical success (OR 4,47, 95% CI 1,17–17,08, p=0,02). The detailed results are shown in Table 5.

Table 5. Odds ratio of retained variables associated with clinical success in multivariate logistic regression analysis

CI = confidence interval; C/T = ceftolozane/tazobactam; OR = odds ratio

Variable	OR	95% CI	p value
C/T therapy	4,47	1,17 - 17,08	0,02
Age	0,94	0,89 - 1,01	0,06

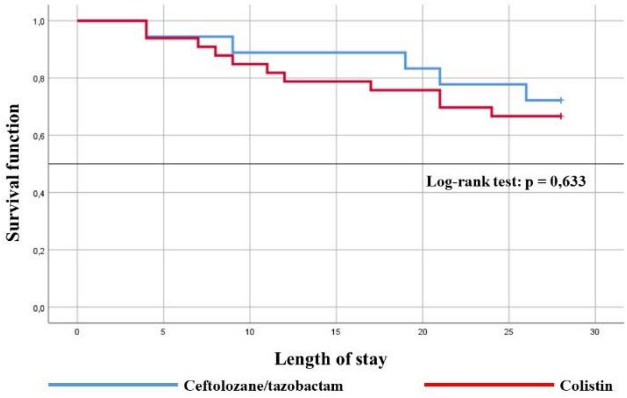

Fig. 6.
Kaplan-Meier survival analysis in the ceftolozane/tazobactam and colistin groups.

28-day all-cause mortality rate was 5 (27,8%) in the C/T, and 11 (33,3%) in the CMS group (p=0,76). Estimated

Kaplan–Meier survival curves showed that patients on C/T treatment tends to have a higher survival rate than those on CMS treatment (Figure 6.). No statistical difference was demonstrated by the log-rank test (p=0,63).

4.4.3. Adverse events

The incidence of at least one adverse event 10 out of 18 patients (55,5%) in the C/T group, and 24 out of 33 patients (72,7%) in the CMS group. The most frequently documented adverse events are shown in Table 6. Acute kidney injury was signifcantly more common in patients who received CMS: 16 patients (48,5%) experienced AKI in the CMS group and 2 patients (11,1%) in the C/T group (p=0,01).

Table 6. Adverse events in colistin and cefolozane/tazobactam treated patient groups.

ALAT = alanine-aminotransferase; ALP = alkaline phosphatase; ASAT = aspartate-aminotransferase; CMS = colistimethate sodium; C/T = ceftolozane/tazobactam; GGT = gamma-glutamyl-transferase [a]$\chi 2$ test or Fisher's exact test *p < 0,05

Adverse event	CMS group n = 33	C/T group n = 18	p value
***Clostridioides difficile* colitis**	3 (9,1%)	0 (0%)	0,54[a]
Diarrhoea	7 (21,2%)	2 (11,1%)	0,46[a]
Vomiting	10 (30,3%)	2 (11,1%)	0,17[a]
Atrial fibrillation	8 (24,2%)	3 (16,7%)	0,72[a]
Erythema	5 (15,2%)	1 (5,5%)	0,40[a]
Acute kidney injury	16 (48,5%)	2 (11,1%)	0,01[a]*
Increased ASAT	6 (18,2%)	4 (22,2%)	0,72[a]
Increased ALAT	8 (24,2%)	5 (27,8%)	1,00[a]
Increased GGT	11 (33,3%)	3 (16,7%)	0,32[a]
Increased ALP	8 (24,2%)	1 (5,5%)	0,13[a]

5. CONCLUSIONS

1. We were the first in Hungary to demonstrate an effective VAP bundle reflected by the improved compliance to preventive measures, and by the reduced risk and decreased incidence of VAP.
2. We found nursing care processes, multidisciplinary approach and education as important factors in VAP prevention.
3. Our findings on long-term knowledge retention would seem to imply that a refresher educational session within 12 months after implementation may be beneficial.
4. Our study of the hand hygiene practice revealed two major risk factors of developing VAP. Low compliance rate was observed among ICU doctors, and to two moments when hand hygiene is required: before touching the patient, and after touching patient surroundings.
5. Our results indicate the possible role of the hand-held scanner technology in achieving and maintaining appropriate hand disinfection.

6. We were the first in Hungary to report that treatment with ceftolozane/tazobactam is independently associated with clinical cure of VAP due to XDR *Pseudomonas aeruginosa*. Furthermore, ceftolozane/tazobactam is a safe option in avoiding nephrotoxicity compared to colistin.

6. BIBLIOGRAPHY OF THE CANDIDATE'S PUBLICATIONS

6.1. Publications included in the thesis

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III. **Mogyoródi B**, Szabó M, Dunai E, Mester B, Hermann Cs, Gál J, Iványi Zs. Azonnali visszajelző rendszer bevezetése a kézhigiéné gyakorlatába intenzív osztályon [Implementation of immediate feedback system into hand hygiene practice in the intensive care unit] **ORVOSI HETILAP** 160: 49 pp. 1957-1962. (2019) Scopus - Medicine (miscellaneous) SJR indikátor: Q3
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IV. **Mogyoródi Bence**, Csékó András B, Hermann Csaba, Gál János, Iványi Zsolt D. Ceftolozane/tazobactam versus colistin in the treatment of ventilator-associated pneumonia due to extensively drug-resistant Pseudomonas aeruginosa. **SCIENTIFIC REPORTS** 12: 1 Paper: 4455, 10 p. (2022) Scopus - Multidisciplinary SJR indikátor: D1
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6.2. Other publication by the author

Varga T[1], **Mogyorodi B**[1], Bago AG, Cservenak M, Domokos D, Renner E, Gallatz K, Usdin TB, Palkovits M, Dobolyi Árpád. Paralemniscal TIP39 is induced in rat dams and may participate in maternal functions. **BRAIN STRUCTURE & FUNCTION** 217: 2 pp. 323-335. (2012) [1]The first 2 authors contributed equally to this work.
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