

Extended infusion versus intermittent infusion of imipenem in the treatment of ventilator-associated pneumonia

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Background: Mechanical ventilation support can be the main source of ventilator-associated pneumonia (VAP). VAP is a serious infection that may be associated with dangerous gram-negative bacteria mainly, and it leads to an increase in the mortality in the intensive care unit (ICU). Imipenem is one of the strongest antibiotics now available for treating VAP which is associated with gram-negative and gram-positive bacteria, and it belongs to beta-lactam antibiotic group (carbapenem).

Objective: This study tried to investigate the efficacy of imipenem against VAP when it was infused within 180 min versus the efficacy when it was infused within 30–60 min.

Setting: This study was conducted in main ICU in general hospital which consists of surgical and medical beds within 2 years. One hundred and eighty-seven patients were enrolled on it.

Method: This study is a retrospective cohort which was conducted within 2 years. The efficacy of imipenem which was administered by intermittent infusion (30–60 min) within first year was compared with the efficacy of imipenem which was administered by extended infusion (180 min) within second year in the field of VAP curing and cost reduction. All data were collected retrospectively from patient medical files and were statistically analyzed by SPSS version 20.

Main outcome: The study was designed to measure clinical and cost reduction outcomes, mortality and hospital stay.

Results: The results indicated that there is a significant decrease in mortality, number of recurrent infection, and ICU stay length, and the number of mechanical ventilator days was associated with extended imipenem infusion during the second year of the study.

Conclusion: The use of imipenem with extended infusion over 3 hours enhances its clinical outcomes in the treatment of VAP.

Keywords: carbapenem, imipenem, VAP, extended infusion, intermittent infusion

Introduction

Ventilator-associated pneumonia (VAP) is a serious form of lung infection among intensive care unit (ICU) patients that results from mechanical ventilation support.¹ Also, it is a major source of mortality among these critically ill patients with rates as high as 24%–76% reported at a variety of institutions. Critically ill ventilated patients with VAP have (2–10)-fold higher risk of death compared with patients without VAP. VAP complicates the course of treatment for patients (8%–28%) who receive mechanical ventilation,^{2–4} and it can be diagnosed by a combination of several radiographic, clinical, and laboratory evidences,^{5,6} such as body temperature greater than 38.3°C or less than 36°C, white blood cell count greater than 10,000/mm³ or less than 4,000/mm³, purulent secretions, increased secretions, or change in secretions.

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Also, positive tracheal cultures or bronchoalveolar lavage (BAL) cultures can be used for diagnosis of VAP.⁷ Moreover, VAP can be diagnosed with some signs of respiratory distress, such as shortness of breath, rapid breathing, and abnormal breathing sounds when listening by chest auscultation, increased need for oxygen on the ventilator, and at least two serial chest's X-rays showing sustained or worsening shadowing (infiltrates or consolidations).

Gram-negative bacterial infections are a very important issue in health care-associated infections, especially in pneumonia caused by VAP.^{8,9} Many studies have demonstrated a significant relationship between VAP attributed to multidrug-resistant gram-negative bacteria (MDR-GNB) and greater mortality rates.^{10–12} Furthermore, MDR-GNB is more likely to be treated with an inappropriate initial antibiotic regimen, which in part explains the higher mortality rate associated with these infections.^{13,14} According to our ICU settings microorganism occurrence, the gram-negative bacteria are the leading source of VAP infections. This finding is in parallel with other worldwide data in the same infection area.¹⁵ In this study, a combination of imipenem with cilastatin, which has high efficacy to gram-negative bacteria, was used according to our antibiogram. Imipenem is a member of carbapenem group with broad spectrum activity against gram-positive and gram-negative bacteria. Therefore, imipenem is used in empirical therapy to a lot of infection caused by different bacteria.^{16,17} Infectious Diseases Society of America (IDSA) reported that extended infusion is an ideal way to optimize beta-lactams antibiotic efficacy.¹⁸ The activity of imipenem, like other beta-lactams antibiotic, depends on the time of infusion. Therefore, this study compared the efficacy of imipenem when used as intermittent infusion and also when used as extended infusion to figure out if this recommended method has any clinical impact both in curing VAP and also in total cost reduction or not.

Aim of the study

To investigate the clinical and cost reduction efficacy of imipenem against VAP when it was infused within 180 min versus the efficacy when it was infused within 30–60 min and its impact on mortality and hospital stay.

Ethics approval

This study is a retrospective cohort study; in this type of study, formal consent is not required. All data were collected from patients' files without any interference in patient treatment plans. As this is a retrospective cohort study, the Ethics Committee of Minia University judged that it did not require ethical approval and patient consent, and also

patient confidentiality has been maintained; all data were anonymized.

Method

This study is a retrospective cohort study on adult ICU patients with VAP. The study was conducted in 25-beds ICU which consists of 14 medical beds and 11 surgical beds in a general hospital. The 2-year study period was between January 2013 and December 31, 2014. All data were collected from antimicrobial approval sheet; patient medical file which had all information about infection, mortality, and hospital admission and stay records; and patient daily progress sheets. Data collected before December 31, 2013, were compared with data that collected after December 31, 2013, until December 31, 2014. The data were analyzed by IBM SPSS program version 20.

In period between January 2013 and December 2013, most of the patients received imipenem to treat VAP by intermittent infusion; on the other hand, in the period between January 2014 and December 2014, most of the patients received imipenem by extended infusion. So, our study objective is to investigate which method will be more effective clinically and financially.

Patient

In the study period, 891 patients with VAP were scrutinized and dispositioned based on inclusion criteria where 563 patients had gram-negative and 509 patients had gram-negative organisms sensitive to imipenem, and only 187 patients fulfilled all inclusion criteria for study.

Antimicrobial agent

The only carbapenem used in this study was imipenem with cilastatin which came with agreement from our local epidemiology antibiogram for highest sensitivity for gram-negative bacteria. Imipenem dose is 500 mg every 6 hours or 1 g every 3 hours, not exceeding 4 g per day. The lower dose was used in patients less than 70 kg and with renal impairment, and same dose regimen was administered to both groups, see Table 1.¹⁹ Imipenem plasma protein binding is 13%–21%, and cilastatin plasma protein binding is 40%. Imipenem is

Table 1 Adjustment of imipenem 1.5 g per day dose for renal impairment patients with weight 40 kg

	CrCL (mL/min/1.73 m ²)	Dose (mg)	Intervals (h)
1	≥71	250	8
2	41–70	125	6
3	21–40	125	8
4	≤20	125	12

Table 2 MIC of imipenem range for gram-negative bacteria

Organism	<i>Pseudomonas</i>	<i>Klebsiella</i>	<i>E. coli</i>	<i>Acinetobacter</i>	Others
MIC ($\mu\text{g/mL}$) of imipenem	0.5–4	0.06–0.5	0.06–0.25	1–8	0.25–8

metabolized in the kidney by dehydropeptidase-1 whose activity is blocked by cilastatin. The half-life of both drugs is 60 min, and it is prolonged with renal impairment. It was reported that 70% of unchanged drug was excreted in urine (both drugs).^{20–22}

Microorganism prevalence

In total, 386 isolates were gram-negative infection with MIC range, which are shown in Table 2 and prevalence percentage to each organism shown in Table 3.

Inclusion criteria

- Patients were diagnosed with VAP.
- Patient had VAP caused only by gram-negative bacteria and sensitive to imipenem or intermediate with no sensitivity to other antibiotics screened in the extended infusion period.
- Patients started imipenem within 48 hours after culture sensitive for imipenem.
- Patients started imipenem empirically, and culture results came with gram-negative pathogens which were sensitive to imipenem, so patients continued on imipenem.
- Patients started course of treatment on imipenem over 4 days.

Exclusion criteria

- Isolates that showed resistance to imipenem.
- Patients start any beta-lactam for treatment of VAP and shifted to imipenem before culture.
- Patients start on intermittent or at take one dose by intermittent infusion in the period of the extended infusion.
- Patients with multiple organisms covered by other drug(s) with imipenem.
- Patients with VAP caused by organisms other than gram-negative.

Table 3 Gram-negative bacterial prevalence during study

Microorganism isolates prevalence %	Extended infusion period (%)	Intermittent infusion period (%)	P-value
<i>Pseudomonas</i> species	28	25	0.82
<i>Klebsiella</i> species	35	29	0.76
<i>E. coli</i>	18	22	0.80
<i>Acinetobacter</i> species	11	15	0.78
Other gram-negative bacteria	8	9	0.85

- Patients with no culture on starting (empirically) and no growth and no culture after 3 days.
- Patients who started imipenem after 48 hours after positive culture sensitivity for imipenem.
- Patients who did not complete 4 days from starting imipenem.
- Patients allergic to imipenem or cilastatin.

Results

In the present study, 187 patients were fit for inclusion criteria. Patients' age was between 29 and 76 years old; the number of female was 86 patients and patient BMI was between 18 and 48. In total, 124 patients were from Middle East, 59 patients were Asian, and 4 patients had other ethnicities, as shown in Table 4.

Table 4 Demographic data

Demographic data	Extended infusion	Intermittent	P-value
Age (year)	55 \pm 11.4	61 \pm 14.2	0.76
Gender (female)	47 (48)	39 (44)	0.79
Ethnicity			
Middle East	63 (64)	61 (68.5)	0.77
Asian	32 (33)	27 (30.3)	0.75
Others	3 (3)	1 (1.2)	0.06
BMI	24 \pm 3	22.5 \pm 2.9	0.66
Comorbidities			
Respiratory (not VAP)	14 (14)	11 (12)	0.70
Cardiovascular	33 (34)	35 (39)	0.69
Immunodeficiency	3 (3)	1 (1)	0.07
CNS	2 (2)	4 (4)	0.08
Oncology	1 (1)	1 (1)	0.65
Hematology	7 (7)	5 (6)	0.77
Liver	24 (24)	18 (20)	0.43
Renal	29 (30)	22 (25)	0.5
Baseline SOFA score	11.34 \pm 1.98	10.95 \pm 1.78	0.85
Patient start empirically with inclusion criteria	42 (43)	38 (43)	0.84
Days in ICU before developing VAP (days)	3.98 \pm 1.32	4.45 \pm 1.66	0.83
Site of sample taking for screening VAP infection			
ETT or tracheostomy tube	28 (29)	31 (35)	0.79
Sputum	46 (47)	39 (44)	0.79
BAL	21 (21)	15 (17)	0.82
Others	3 (3)	4 (4)	0.85
Patients who had more than one gram-negative organism all sensitive to imipenem	25 (26)	18 (20)	0.79

Note: Data presented as mean \pm standard deviation or n (%).

Abbreviations: BMI, Body Mass Index; VAP, ventilator associated pneumonia; CNS, central nervous system; SOFA, Sepsis-related Organ Failure Assessment score; ICU, intensive care unit; ETT, endotracheal tube; BAL, broncho-alveolar lavage.

Table 5 Clinical outcomes of study results

Outcome data	Extended infusion (n=98)	Intermittent (n=89)	P-value
Mortality	4 (4)	18 (20)	0.03
Recurrent infection with the same organisms	2 (2)	13 (14)	0.04
ICU stay (days)	9.59±2.12	15.34±3.75	0.04
Mechanical ventilator (days)	9.32±2.3	15.11±3.78	0.045
Cost related to infection (\$)	5,430±893	9,800±1,345	0.31
Total hospital cost (\$)	10,110±1,853	18,330±4,854	0.26

Note: Data presented as mean ± standard deviation or n (%).

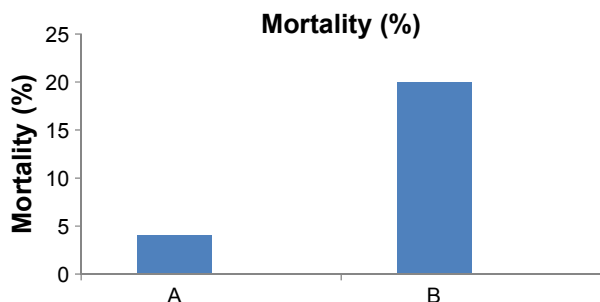
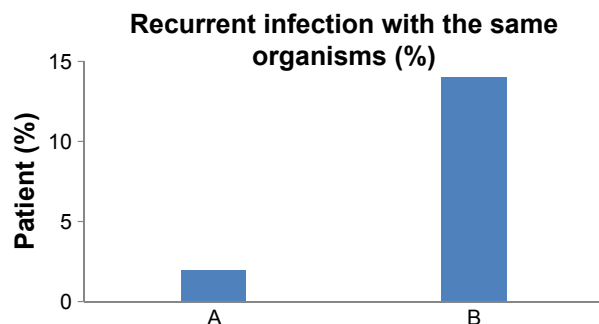
Cardiovascular, renal, and hepatic problems were the most common comorbidities associated with patients in the two study groups, and also most common site of sample collection was ETT, tracheostomy tube, sputum, and BAL, as shown in Table 4.

Baseline SOFA score (Sepsis-related organ failure assessment score) for intermittent infusion patients was 11.34±1.98 but baseline SOFA score for extended infusion patients was 10.95±1.78, as shown in Table 4.

About mortality, only 4 patients died by VAP during the second year (extended infusion), compared to 18 patients during the first year (P -value =0.03), see Table 5 and Figure 1.

Only 2 patients had rebound infection compared to 13 patients during the first year (P -value =0.04) as shown in Table 5 and Figure 2. Furthermore, ICU stay during the second year was 9.59±2.12 days compared to 15.34±3.75 days during the first year (P -value =0.04), as shown in Table 5 and Figure 3. Finally, the mechanical ventilation duration time during the second year was 9.32±2.3 days compared to first year (15.11±3.78) days with P -value (0.045); the details are shown in Table 5 and Figure 4.

The cost related to infection per patient at the second year was 5,430±893 USD whereas at the first year was 9,800±1,345 USD, as shown in Table 5 and Figure 5. The total

**Figure 1** Percentage of mortality: (A) extended infusion, (B) intermittent infusion.**Figure 2** Percentage of patients who had recurrent infection with the same microorganism.

Note: (A) extended infusion, (B) intermittent infusion.

hospital cost per patient at the second year was 10,110±1,853 USD whereas at the first year was 18,330±4,854 USD; the details are shown in Table 5 and Figure 6.

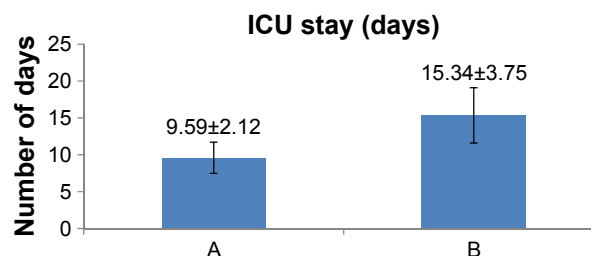
Discussion

In our hospital settings, antimicrobial resistance especially for gram-negative bacteria was dramatically increased. Innovative policies and technique like enhancing PK/PD and antibiotic cycling were implemented to inhibit antimicrobial resistance and increasing antibiotic efficacy. In the present study, we evaluate the benefits of increasing infusion time to be extended infusion rather than intermittent infusion to enhance antibiotic pharmacodynamics. These approaches were approved by many studies. Beta-lactams are time-dependent antibiotics, and their activity increases by increasing exposure time.²³

In this 2-year study, at the first year (1 January to 31 December 2013), beta-lactam antibiotic (carbapenem and imipenem) had been used by intermittent 30–60-min infusion, whereas at the second year (1 January to 31 December 2014) beta-lactam (imipenem) had been used by extended infusion over 3-hours infusion.

Non-significant difference was observed between 2 years in baseline SOFA scores (P -value =0.85), this means that the two study arms had patients in same ill status conditions.

Non-significant difference was observed between the groups of the study in age, gender, ethnicity background,

**Figure 3** ICU stay (days): (A) extended infusion, (B) intermittent infusion.

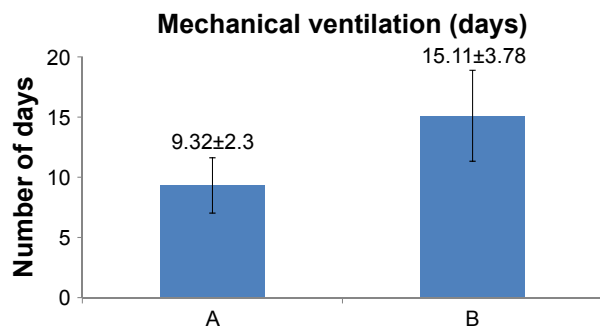


Figure 4 Mechanical ventilation (days): (A) extended infusion, (B) intermittent infusion.

and BMI, this indicates that the patients in two groups had the same demographic features.

Non-significant difference was found between the two groups in the number of samples which were collected from sputum, BAL, ETT, tracheostomy tube, and other sites. A non-significant difference was found between the two groups in the number of patients who started imipenem as empirical therapy with same inclusion criteria, in number of days before the development of VAP, and in number of patients who had more than one gram-negative bacteria and sensitive to imipenem.

Non-significant difference was found between the two groups in percentage of prevalence of different gram-negative species whereas more prevalent ones were *Pseudomonas* species, *Klebsiella* species, and *E. coli* and *Acinetobacter* species, as shown in Table 3 and Figure 7; this approved that almost the two study arms had same preexisting conditions.

The clinical results revealed a significant decrease in mortality rate with second year, often this was due to improving in VAP condition; these results agree with results observed by Lodise TP who performed a cohort study of patients who received piperacillin-tazobactam therapy for a *Pseudomonas aeruginosa* infection that was susceptible to piperacillin-tazobactam during the period January 2000 to June 2004. Prior to February 2002, all patients received

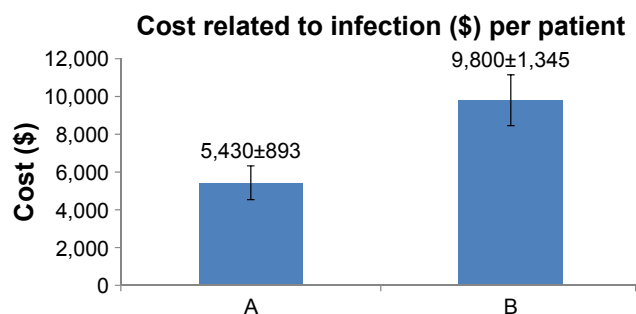


Figure 5 Cost related to infection per American dollar per patient. Note: (A) extended infusion, (B) intermittent infusion.

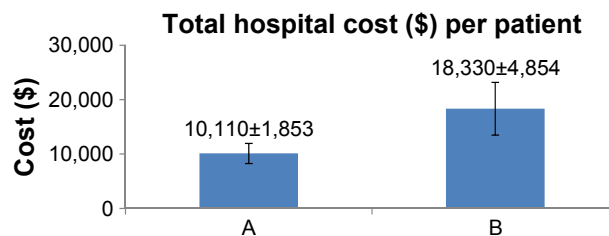


Figure 6 Total hospital cost reduction per American dollar per patient. Note: (A) extended infusion, (B) intermittent infusion.

intermittent infusions of piperacillin-tazobactam (3.375 g intravenously for 30 min every 4 or 6 hours); after this time, all patients received extended infusions of piperacillin-tazobactam (3.375 g intravenously for 4 hours every 8 hours) and results observed Yost who stated that pharmacodynamic dosing using extended-infusion piperacillin-tazobactam demonstrated favorable outcomes, including mortality, when compared with nonextended-infusion, similar-spectrum beta-lactams in the treatment of patients with documented gram-negative infections.^{24,25}

Significant decrease in rebound infection by the same microorganism was reported during the second year; this is because of increasing the efficacy of imipenem in gram-negative bacteria eradication.

Significant decrease in ICU stay length which was caused by VAP infection with second year, a significant decrease was in mechanical ventilation days during second year was reported when compared with same results at first year and a non-significant decrease in cost either related or not related between 2 years were reported, all these findings are due to increasing efficacy of imipenem in the treatment of VAP. These results strongly agree with results which observed in hospital stay-related infection by Nicasio et al who concluded that in their ICUs where multidrug-resistant bacteria are common, an approach considering ICU-specific antibiotic MICs coupled with pharmacodynamic dosing strategies resulted in improved outcomes and shorter duration of treatments.²⁶

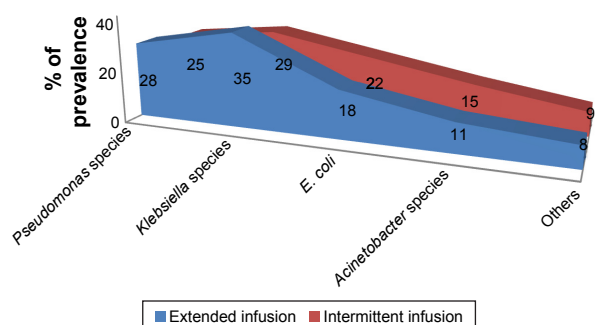


Figure 7 Prevalence for gram-negative bacteria.

Conclusion

Extended infusion was implemented to improve the PK/PD profile of imipenem as a means to maximize its therapeutic benefit against imipenem-responsive gram-negative-caused VAP in our ICU facility. Significant reduction of mortality rates, infection duration, mechanical ventilation time, and ICU stay length with the new extended infusion protocol when compared to the previous intermittent infusion protocol was achieved. This approach can therefore be recommended to treat VAP on a wider health care scale.

Disclosure

The authors report no conflicts of interest in this work.

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