Evaluation of Alone or Combined Colistin Therapy Success in Patients with Carbapenem-Resistant Acinetobacter Pneumonias

Karbepenem Dirençli Acinetobacter Pnömonilerinde Tek Başına veya Kombine Kolistin Tedavisi Başarısının Değerlendirilmesi

Acinetobacter Pnömonisinde Kombine Kolistin / Combined Colistin in Acinetobacter Pneumonia

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Özet

Amaç: Karbepenem dirençli gram negatif bakteri yoğun bakım ünitelerinde artan bir tehlikedir. Kliniğimizde acinetobacter enfeksiyonunda farklı tedavi rejimlerinin ve mortalite oranlarının sonuçlarını saptamayı amaçladık. Kombine kolistin tedavisi üstün mü, değil mi? Gereç ve Yöntem: Ocak 2013 ve Haziran 2014 tarihleri arasında kliniğimizde tanı konulmuş ve tedavi edilmiş, acinetobacter enfeksiyonu olan 23 olgu, tedavileri ve mortalite süreleri yönünden retrospektif olarak incelenmiştir. Bulgular: 23 hastanın 19'u yoğun bakımda, 4'ü serviste tedavi edilmiştir. Yoğun bakım ünitesindeki 19 hastadan; sefoperazon+sulbaktam duyarlı olan grupta 2 hasta, sefoperazon+sulbaktama da duyarlı olmayan grupta 3 hasta kolistin monoterapisi ile exitus oldular. Kombine tedavi alan hastalar arasında, 2 olguya amikasin+kolistin kombine tedavisi verildi; bu iki hasta da exitus oldular. Kolistin+rifampisin kombine tedavisi alan bir olgu da iyi yanıt alındı. Serviste tedavi edilen 4 hastanın 3'ü karbapenem dirençliydi ve bunlardan da 1'i sadece kolistine duyarlıydı. Bu hasta, kolistin+tigesiklin kombine tedavisi aldı ve iyi yanıt elde edildi. Tartışma: Akciğerin acinetobacter enfeksiyonlarında mortaliteyi azaltmak için kombine kolistin tedavisi yararlı görünmektedir. Karbapenem dirençli acinetobacter olgularının rifampisin ve tigesiklin kombinasyonu açısından değerlendirilmesi gerektiği görüşündeyiz.

Anahtar Kelimeler

Acinetobacter; Rifampisin; Tigesiklin

Abstract

Aim: Carbapenem-resistant gram negative bacteria represent an increasing problem worldwide for intensive care units. We aimed to detect the outcome of different treatment regimens and mortality rates of Acinetobacter infection in our clinic. Is combined colistin therapy superior or not? Material and Method: 23 cases diagnosed and treated in our unit with documented Acinetobacter infections between January 2013 and June 2014 were retrospectively evaluated in terms of treatments administered and mortality rates. Results: 19 of 23 patients were treated in ICU and 4 of 23 patients were treated in normal patient ward. Among 19 ICU patients, 2 patients in cefoperazone + sulbactam - susceptible groups and 3 patients with cefaperazone + sulbactam - resistant groups died with colistin monotherapy. Among patients receiving combined treatment, two patients were given amikacin + colistin combination and they both died. A single patient receiving colistin + rifampicin combination responded well. Of the 4 patients treated in the normal patient ward, 3 had carbapenem resistance, and of these, only 1 was susceptible to colistin. This patient received colistin + tigecycline combination and had good response. Discussion: The combined colistin treatment seems plausible in terms of reducing mortality in Acinetobacter infections of lung. We believe that in patients with carbapenem-resistant Acinetobacter infections, a consideration should be given to rifampicin or tigecycline combination with colistin.

Keywords

Acinetobacter; Colistin; Rifampicin; Tigecyclin

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Introduction

Infections due to carbapenem-resistant gram negative bacteria (CRGNB) represent an important problem worldwide, and the main question regarding the treatment of this patient group is whether a combination treatment or monotherapy should be administered. Despite some reports suggesting a superiority of combination regimens over colistin monoteraphy in CRGNB infections, therapeutic guidelines provide no definitive approach in such cases [1]. After the initial observations suggesting better outcomes in patients with pneumonia due to carbapenem-resistant Acinetobacter who were treated with combined regimens, we decided to undertake a study comparing different regimens in our clinic and assessing effect of combined treatment and monotherapy on morbidity and mortality.

Material and Method

Patients diagnosed and treated in our unit with documented Acinetobacter infections between January 2013 and June 2014 were retrospectively evaluated in terms of treatments administered and mortality rates. Of the 23 cases overall, 19 were treated in the intensive care unit, whereas 4 were admitted to normal patient ward. Microbiological cultures were obtained and antibiograms were performed in tracheal aspiration or sputum samples. Mortality, time to mortality, growth in microbiological samples, time to documented absence of growth in sputum samples, c-reactive protein (CRP) measurements, fever, and duration of follow-up after discharge were recorded. Due to small sample size formal statistical tests were not performed.

Results

All cases, i.e. 19 patients, with Acinetobacter infections in the intensive care unit subsequently proved to have ventilator - associated pneumonia. Among the isolated species from these 19 patients, only 2 (11%) were susceptible to carbapenem. Therefore, these two patients responded to a course of carbapenem and have now completed 1 year of follow - up.

Of the 17 cases (89%) with carbapenem - resistant Acinetobacter infection, 11 (64%) were susceptible to cefaperazone + sulbactam. Among these 11 cases with cefaperazone + sulbactam - susceptible but carbapenem- resistant cases, 2 died following colistin monotherapy, while 2 died before a treatment was given. Of the latter two cases, the results of the sputum cultures could only be available on the day of death precluding any treatments. Of these 11 patients with cefaperazone + sulbactam-susceptible but carbapenem - resistant infection, one died despite treatment with cefaperazone + sulbactam. Following CRP and clinical response, this case had resurgence of CRP, and probably died after a new infection before the causative agent was detected. In 6 of the 11 cases with cefoperazone + sulbactam - susceptible but carbapenem - resistant infection, a response to cefoperazone + sulbactam could be obtained with subsequent discharge.

The remaining 6 cases (35%) with carbapenem - resistant Acinetobacter had cefoperazone + sulbactam resistant infection. Of these, 4 were susceptible to colistin only (percentage of cases with carbapenem - resistance and exclusive colistin - susceptibility, 24%) while 2 also had amikacin susceptibility.

Of the 6 cases with carbapenem - resistant and cefoperazone + sulbactam resistant Acinetobacter infection, one received colistin + rifampicin combination, who had no growth in the sputum culture on day 8, with reduction in CRP and subsequent discharge. The patient has now completed 1 - year of follow-up. The second case died on the first day of colistin monotherapy. The third case received colistin + amikacin due to susceptibility to both amikacin and colistin. Although there was no growth on day 3 of the treatment, CRP did not decrease and no clinical response to treatment was observed. A repeat sputum culture revealed meticilline - resistant Staphylococcus aureus (MRSA) and the patient died on the day of documented MRSA. This patient also had signs of renal failure. The fourth case had amikacin susceptible Acinetobacter infection and received colistin + amikacin combination. On Day 9 of the treatment there was no growth in the sputum culture, despite no decrease in CRP. This patient also died. The fifth case received colistin monotherapy, with no CRP response and no growth in sputum culture on Day 4. He developed renal toxicity and electrolyte disturbance, attributed to antibiotic treatment, and died following cardiac arrest. Again, microbiological growth was detected in the sixth case on the day the patient died due to cardiac arrest developing at Day 1 of treatment. Table 1 shows the treatments and mortality in patients with carbapenem - resistant Acinetobacter infection.

Table 1. The treatments and mortality in patients with carbapenem-resistant Acinetobacter infection in intensive care unit

Case	Threat-ment	Sputum culture	CRP response	Complica-tions	Mortality	Mortality day*	Follow-up
1.	colistin + rifampicin	8.day, no m.o.	yes	no	no	-	1-year of follow-up
2.	colistin	-	-	-	yes	1.day	
3.	colistin + amikacin	3.day, no acineto-bacter, but MRSA	no	renal failure	yes	5.day	
4.	colistin + amikacin	9.day, no m.o.	no	no	yes	9.day	
5.	colistin	4.day, no m.o.	no	renal failure / electrolyte disturbance	yes	4.day	
6.	colistin	-	-	-	yes	1.day	

*: after threatment
**: m.o: microorganisms
CRP: C-Reactive Protein
MRSA: Methicillin-resistant Staphylococcus aureus

Of the 4 patients admitted to the normal patient ward, 3 had carbapenem resistant Acinetobacter. One of these cases had meropenem susceptible infection and he was receiving concomitant antituberculous treatment. He is currently being followed - up by an outpatient tuberculosis clinic. Two patients had cefoperazone + sulbactam susceptible infections and were discharged following successful treatment with cefoperazone + sulbactam. Among the three carbapenem-resistant cases in the normal patient ward group, one only had colistin susceptibility and received colistin and tigecycline. The patient was also receiving concurrent hemodialysis. At day 10 there was no growth in

the sputum culture and he was eventually discharged. All patients who received combined colistin therapy or colistin monotherapy are listed in Table 2.

Table 2. The treatments and mortality in patients who receive combined colistin therapy or colistin monotherapy

Threatment		intensive care unit		normal patient ward**	Mortality	Total
		cefaperazone + sulbactam-susceptible	cefoperazone + sulbactam resistant			
mono therapy	colistin	2 case	3 cases*	-	yes	5 cases
combined therapy	colistin/ amikacin	-	2 cases	-	yes	4 cases
	Colistin/ rifampicin	-	1 case	-	no	
	colistin/ tigecycline	-	-	1 case	no	

*: Two cases died on the first day of colistin monotherapy
**: One patients had karbapenem and cefoperazone + sulbactam resistant infections. The other 3 patients in normal patient ward had karbapenem or cefoperazone + sulbactam susceptible and were discharged following successful treatment with karbapenem or cefoperazone + sulbactam.

Discussion

In a recent review examining the treatment of Acinetobacter infections, three studies have been found that demonstrated a superiority of combination treatment over monotherapy in multiple-drug resistant Acinetobacter including carbapenem. The authors have concluded that combined treatment may be recommended for severe disease [2]. In our patient group, 5 subjects had monotherapy as compared to 4 patients receiving combined treatment. Of the combinations, 2 involved amikacin, and one of these patients died with electrolyte disturbances and renal toxicity. One case had colistin plus rifampicin and 1 had colistin plus tigecycline combination, with good response. On the other hand, all of the five patients receiving monotherapy died.

Again in another recent publication, the lack of data demonstrating the efficacy of combination therapy has been emphasized, despite the common use of combinations in the clinical practice [3]. In that paper, data obtained across 28 Spanish hospitals were analyzed. Most of the patients involved in the assessment were receiving mechanical ventilation (68.6%) and the most common type of infection was pneumonia (50.5%). The agents that were most commonly used in combinations were colistin (67.6%) and carbapenem, while the combination utilized with the highest frequency was colistin-tigecycline (27.3%). The observed 30 - day mortality rates in monotherapy and combination therapy were 23.5% an 24.2% (p = 0.94), showing no mortality benefit with combination. On the other hand, among our patients with carbapenem resistant Acinetobacter who received colistin (n = 9), one (11.1%) had colistin plus tigecycline and one (11.1%) had colistin plus rifampicin, and both cases responded well to these regimens. The mortality rate in 5 patients (55%) receiving monotherapy was 100%. Although it is not possible to draw firm conclusions due to small sample size, our observations suggest a better efficacy for the combination.

Conclusion

In multiple drug resistant Acinetobacter pneumonia the mortality rate is high and colistin currently represents the last resort. A consideration should be given to rifampicin plus tigecycline combination in carbapenem resistant Acinetobacter infections. Further studies are warranted to better define the role of combinations and to establish standard protocols.

Authors' contributions: ÖED planned the study, collected data and wrote the paper. AT and SA helped to collect data and write the paper.

Competing interests

The authors declare that they have no competing interests.

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