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Articolo originale

Original article

A nightmare for haematology clinics: extensively drug-resistant (XDR) *Acinetobacter baumannnii*

Acinetobacter baumannii *XDR: un incubo per i reparti di ematologia*

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INTRODUCTION

Acinetobacter baumannii became an endemic pathogen in the intensive care units (ICU) of our hospital after several outbreaks, and more than 70% of the isolates are extensively drug-resistant resistant (XDR) [1, 2]. Since patient transfer from ICU is a common practice, it is difficult to prevent the spread XDR *A. baumannii* (XDRAB) to the other clinics in the absence of adequate hand hygiene and adherence to the contact isolation precautions. This situation is particularly of concern for haematology clinics and stem cell transplant centre where the patients can be highly vulnerable to XDRAB without any reliable treatment options.

Between March 2006 and June 2011, we identified 11-haematology patients with *A. baumannii* bacteraemia which were usually ICU-acquired cases [1, 3]. However, the number of the patients with *A. baumannii* infection hospitalized in haematology wards increased till January 2012. Here, we wanted to share our experience on demographic characteristics and clinical outcome of the patients infected with *A. baumannii* in haematology clinics particularly focusing on the period with a sudden increase in the number of XDRAB cases.

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PATIENTS AND METHODS

Erciyes University Hospital is a tertiary care centre which has 38-haematology beds and 30-bed haematopoietic stem cell transplant (HSCT) centre. A patient based infection control programme was set up till 2008, regularly. An infection control nurse (ICN) visited all patients daily. A form including the demographic data and laboratory results were recorded for all patients. In any case of suspicion of an infection, the patient was consulted by an infectious disease (ID) physician. The source of infections was identified according to the criteria proposed by the Centers for Disease Control and Prevention except invasive pulmonary aspergillosis (IPA) which was diagnosed according to European Organization for Research and Treatment of Cancer and the Mycoses Study Group definitons [4, 5].

During the observation period, identification and susceptibility of Gram negative bacilli isolated from cultures were performed by automated systems in accordance with Clinical Laboratory Standards Institute (CLSI) recommendations [6]. Tigecycline susceptibility was determined by disk diffusion and interpreted according to the criteria by the United States Food and Drug Administration (FDA) for *Enterobacteriaceae* [7].

The isolates that were non-susceptible to ≥1 agent in ≥3 antimicrobial categories were defined as multi-drug resistant (MDR), and the iso-

Table 1 - Distribution of personal and disease-related characteristics of the patients with *Acinetobacter baumannii* infection.

Patient characteristics	*Alive (n=6) (%)*	*Dead (n=23) (%)*	*Total (n=29) (%)*
Age (median, range) (years)	34.5 (25-44)	50 (23-79)	54 (23-79)
Male	3 (50)	13 (56.5)	16 (55.2)
Type of haematological malignancy			
Acute myelogenous leukemia	2 (33.3)	11 (47.8)	13 (44.8)
Acute lymphocytic leukemia	2 (33.3)	6 (26.1)	8 (27.6)
Non-Hodgkin lymphoma	1 (16.7)	4 (17.4)	5 (17.3)
Hodgkin Disease	1 (16.7)	2 (8.7)	3 (10.3)
Allogenic stem cell transplantation	1 (16.6)	0	1 (3.4)
Duration from admission to *A. baumannnii* infection (median) (days) (range)	15.5 (7-33)	21 (8-73)	20 (8-73)
Neutrophil counts			
<100 cells/mm^3	3 (50)	19 (82.6)	22 (75.9)
>500 cells/mm^3	3 (50)	4 (17.4)	7 (24.1)
Primary disease status			
Remission	2 (33.3)	2 (8.7)	4 (13.8)
New diagnosis receiving first cycle of chemotherapy	0	10 (43.5)	10 (34.5)
Refractory after first chemotherapy	1 (16.7)	2 (8.7)	3 (11.5)
Relapse after first remission	3 (50)	9 (39.1)	12 (41.4)
Previous history of ICU care	1 (16.7)	2 (8.7)	3 (10.3)
Previous history of carbapenem use	4 (66.7)	21 (91.3)	25 (86.2)
Fungal co-infection	1 (16.6)	3 (13.1)	4 (13.7)
Fungaemia	1	1	
Probable invasive pulmonary aspergillosis*	0	2	
Polymicrobial bacteraemia			3 (10.3)
Pseudomonas aeruginosa	0	2 (8.7)	
Pseudomonas aeruginosa + *Enterococcus* spp.	0	1 (4.3)	
Clinical material where *A. baumannii* isolated			
Blood	5 (83.3)	17 (73.9)	22 (75.9)
Blood + catheter tip	0	1 (4.3)	1 (3.4)
Blood + bronchoalveolar lavage fluid	0	2 (8.7)	2 (6.9)
Blood + endotracheal aspirate	0	1 (4.3)	1 (3.4)
Endotracheal aspirate	0	2 (10)	2 (6.9)
Sputum	1 (16.7)	0	1 (3.4)
Source of *A. baumannii* infection			
Bloodstream	5 (83.3)	18 (78.2)	23 (79.3)
Healthcare associated pneumonia	1 (16.7)	5 (21.8)	6 (20.7)
Multidrug resistant (MDR)	5 (83.3)	23 (100)	28 (96.5)
Extensively drug resistant (XDR)	5 (83.3)	16 (69.5)	21 (72.4)
Antibacterial treatment*			
Empirical	4 (66.6)	4 (17.4)	8 (27.5)
Ampicillin/sulbactam + colistin	1	0	
Piperacillin/tazobactam + tigecycline	0	2	
Meropenem + tigecycline	0	1	
Meropenem	1	0	
Colistin	2	1	
After culture results	2 (33.3)	4 (17.4)	6 (20.7)
Cefoperazone/sulbactam + colistin	1	0	
Sulbactam + colistin	1	0	
Colistin**	1	4	

*Patients were diagnosed with probable invasive pulmonary aspergillosis by clinical-radiological signs and galactomannan antigenemia in serum. **All patients who received colistin monotherapy were already under carbapenem therapy (doripenem, n=1; meropenem, n=3; imipenem, n=4).

lates that were non-susceptible to ≥1 agent in all but ≤2 antimicrobial categories were defined as extensively drug-resistant (XDR) [8].
Since this study was conducted as a part of routine practice of infection control committee, ethics committee approval and informed consent were not required.

RESULTS

Between January 2012 and July 2013, 29 *A. baumannii* infection episodes were detected in 28 patients (one patient had a recurrent bacteraemia after successfully treated first episode). Median age of the patients was 54 years, and 16 of them were male. The most common underlying haematological disease was acute myelogenous leukemia in 13 patients, while the haematological malignancy was relapsing or not under remission in 15 patients, four patients were under remission and 10 patients were newly diagnosed. Twenty two out of 29 patients had profound neutropenia (neutrophil count < 100/mm^3). Three patients had previous history of ICU stay (Table 1).
Blood cultures revealed *A. baumannii* in 26 out of 29 episodes. Susceptibilities to amikacin, netilmicin, and cefoperazone/sulbactam were 13.7%, 41.3%, and 20.7%, respectively. All but one isolate were MDR, and 72.4% (21 out of 29) were XDR. Colistin resistance was detected in one isolate. Tigecycline was active against 8 out of 29 (27.6%) isolates. Polymicrobial bacteraemia with MDR *Pseudomonas aeruginosa* was detected in three patients (Table 1). Colistin was initiated for the treatment in 11 out of 29 episodes. Three patients received colistin combined with sulbactam or sulbactam containing betalactams, the remaining eight patients who received colistin monotherapy were already under carbapenems. Mortality rate (survival status in the following 28 days after index blood culture) was 82.1%. All patients with poor outcome died in the first week after the index blood culture was performed. In 16 out of 29 episodes, the patients died before the culture results became available.

DISCUSSION

XDRAB is a therapeutic challenge for the physicians dealing with immunocompromised patients and has been already listed in the "ESKAPE" pathogens that threaten anticancer treatment efficacy [9]. The mortality rate was significantly high as 82.1% in our patients with several haematological malignancies. The most dramatic part of our observation was primary haematological disease which was under remission or newly diagnosed in 12 out of 23 (52.2%) patients with a poor outcome. All of these patients were candidates for long-term survival according to the response to anticancer therapy.
Off-label tigecycline use was a common practice in the treatment of MDR *A. baumannii* infections based on the *in vitro* susceptibility data in our hospital [10]. In the current analysis, three patients received antimicrobial combination therapy including tigecycline, empirically. Two out of three isolates were susceptible to tigecycline. However, the outcome was poor in three patients who received tigecycline.
Colistin seems to be the only agent for the treatment of XDRAB infections. However, an increase in the MIC of colistin was reported in solid organ transplant patients who were treated by colistin for XDRAB infections. Favourable results for the combination of colistin with carbapenems were reported [11]. The number of the patients included in our observational study was not enough to compare the outcomes based on the type of antimicrobial therapy. Survival rate was higher in the three patients who received colistin plus sulbactam when compared to the patients who received colistin plus carbapenems (Table 1). Nevertheless, these results are based on retrospective data with limited number of patients and need further investigation in prospective controlled trials.
The most concerning finding of this observational study was an increase in the number of the patients with XDRAB infections. To explain this situation we speculated on different theories. Haematological malignancy patients with XDRAB infection (or colonization) who were transferred from ICU to haematology wards could have served as a transporter of XDRAB. The microorganism could have spread by the hands of healthcare staff, shared medical equipment, or patient's companion (usually close relatives of the patient without any medical education). The first cases of XDRAB infection did not receive ICU care, however, between February 01, 2012, and April 30, 2012, two out of six patients who were transferred to haematology clinics and stem cell transplantation centre were infected with XDRAB. After the detection of first cases with XDRAB at the beginning of 2012 (Figu-

re 1), all patients transferred from ICU were strictly isolated regardless of XDRAB infection or colonization status in single rooms. There was an adequate number of lavatories between rooms for the staff to wash their hands before and after contact with the patients. Cautionary cards were placed at the door of the patients' rooms who were infected with any MDR Gram negative or Gram positive bacteria. Alcohol-based hand rinses were available at the bedsides of patients regardless of whether or not they were infected with an MDR bacterium. There was also a routine infection control education programme for all health-care staff twice a year and repeated when XDRAB was isolated at haematology clinics or HSCT centre. Despite these interventions, small clusters of cases with XDRAB infections were detected, and these infection control precautions did not completely prevent the occurrence of new cases (Figure 1). The 24-hour nurse-to-patient ratio (which was calculated by dividing the total number of the nurses working during a 24-hour period by the patients' census of the day) was 0.3 in haematology wards, and 0.6 in HSCT centre [12]. The role of understaffing or uncontrolled behaviors of patient companions should not be disregarded for the increase in the number of XDRAB infections.

Carbapenems were widely used at our haematology clinics as the first-line agent in the treatment of neutropenic fever due to the high prevalence of extended-spectrum beta-lactamase producing *Enterobacteriaceae*, and 86.2% of the patients presented in this paper had a history of carbapenem use in the previous three weeks (Table 1) [3]. Collateral damage of the environment and intestinal flora of the patients by using broad spectrum antibiotics could be responsible for the sporadic cases. The 86.2% (25 out of 29 episodes) of the *A. baumannii* infections were detected from the haematology wards serving more than 10 years, and one out 21 XDRAB infections was recovered from the HSCT centre which is in service for three years (Figure 1). Unfortunately, XDRAB isolates from haematology wards and HSCT centre were not stored, and the lack of clonal analysis of the XDRAB isolates made difficult to understand the exact source. Inadequate adherence to infection control precautions and collateral environmental damage that was caused by prolonged use of carbapenems as the first-line agent in neutropenic fever can be both responsible for the

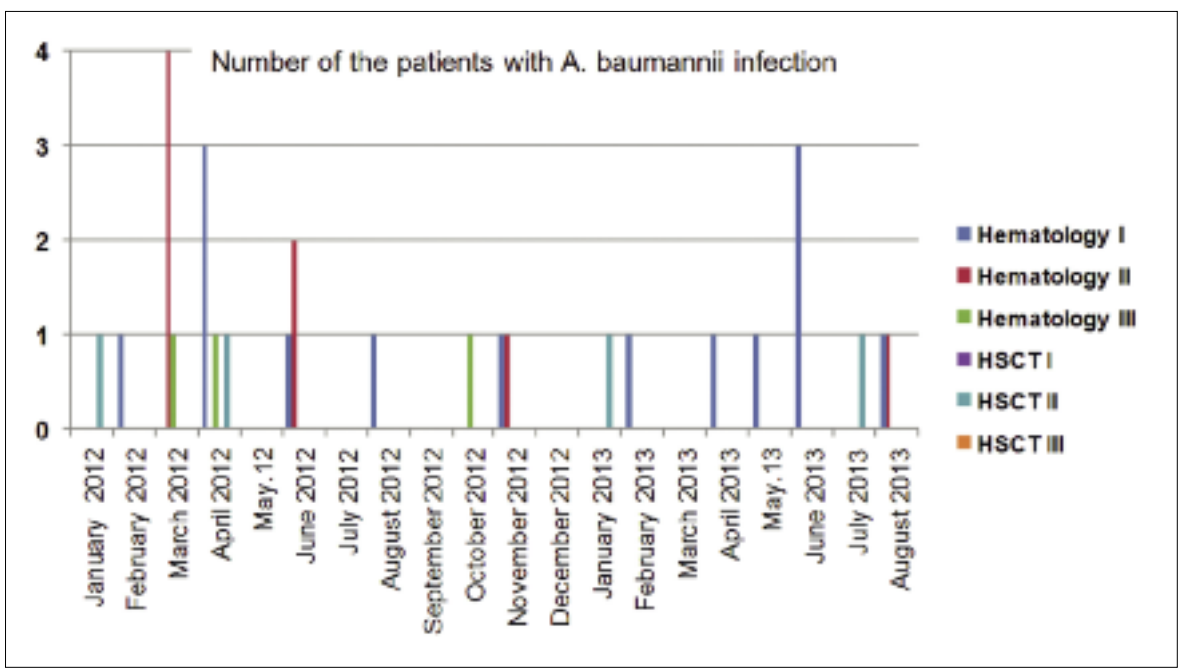

Figure 1 - Distribution of Acinetobacter baumannii infections among haematology wards and haematopoietic stem cell transplantation centre according to the isolation date. Two haematology wards (15 beds each) are located at the same floor divided by a corridor, and the other haematology ward (8 beds) is located at a different floor. Haematopoietic stem cell (HSCT) centre has three wards (9 beds each) located at different floors.

increasing number of XDRAB infections. In summary, XDRAB infections can easily become nightmares of the clinics where immunocompromised patients are hospitalized. Adherence to infection control precautions with an adequate number of healthcare staff should be the priority of the haematology clinics and HSCT centres to prevent of XDRAB. Although the evidence is limited, colistin combined with sulbactam can be a reliable option in the treatment of XDRAB infections particularly when the patients are already under carbapenem therapy.

Conflict of interest: All authors declared any conflict of interest related to this study.

Keywords: *Acinetobacter baumannii*, XDR, haematological malignancy, bacteraemia, febrile neutropenia.

SUMMARY

The purpose of our study was to share experience on demographic characteristics and clinical outcome of the patients infected with extensively drug-resistant *Acinetobacter baumannii* (XDRAB) in haematology clinics, focusing on the period with a sudden increase in the number of XDRAB cases. A regular patient-based infection control programme was set up in haematology clinics and haematopoietic stem cell transplant centre starting from 2008. An infection control nurse visited all patients daily. A form including demographic data and laboratory results were recorded for all patients. The source of infections was identified according to the criteria proposed by the Centers for Disease Control and Prevention. While haematology ward-acquired XRDAB was rare before 2012, between January 2012 and July 2013, 29 *A. baumannii* infection episodes were detected in 28 patients. All but one isolate were MDR and 72.4% (21 out of 29) were XDR. Blood cultures revealed *A. baumannii* in 26 out of 29 episodes. While the haematological malignancy was relapsing or not under remission in 15 patients, four patients were under remission, and 10 patients were newly diagnosed. The mortality rate was 81.2%. All patients with a poor outcome died in the first week after the index blood culture was performed. In 16 out of 29 episodes, the patients died before the culture results became available. Colistin was initiated for the treatment in 11 out of 29 episodes. Three patients received colistin combined with sulbactam or sulbactam containing beta-lactams; the remaining eight patients who received colistin monotherapy were already under carbapenems. In conclusion, XDRAB infections can easily become nightmares for haematology clinics without any reliable treatment option.

RIASSUNTO

Questo studio è stato condotto al fine di condividere la nostra esperienza sulle caratteristiche demografiche e l'esito clinico di pazienti con infezione da Acinetobacter baumannii *panresistente (XDRAB, extensively drug-resistant A. baumannii) ricoverati in reparti di ematologia, rivolgendo l'attenzione soprattutto al periodo in cui si è osservato il maggior numero di casi di infezione da XDRAB.*

Nei reparti di ematologia e nel centro trapianto di cellule ematopoietiche è stato istituito, fin dal 2008, un programma di monitoraggio costante dei casi di infezione nei pazienti (patient based). Un infermiere dedicato effettua l'osservazione quotidiana di tutti i pazienti e la registrazione, su apposito modulo, dei dati demografici e dei risultati di laboratorio. La fonte dell'infezione viene identificata in accordo ai criteri stabiliti dai Centers for Disease Control and Prevention.

Precedentemente al 2012, i casi di infezione da XRDAB osservati nei reparti di ematologia erano scarsi ma nel perido compreso tra gennaio e luglio del 2012, sono stati rilevati 29 episodi di infezione da A. baumannii *in 28 pazienti. Tutti gli isolati, tranne uno, erano* multidrug resistant *(MDR) e il 72,4% (21/29) era XDR. La positivtà delle emocolture per* A. baumanii *è stata registrata in 26/29 episodi. La patologia ematologica era in fase di recidiva, o comunque non in remissione, in 15 pazienti; in fase di remissione per quattro pazienti, mentre per 10 pazienti si trattava di una nuova diagnosi. Il tasso di mortalità è stato pari all'81,2%. Tutti i pazienti con esito sfavorevole sono deceduti nel corso della prima settimana successiva all'esecuzione dell'emocoltura indice. In 16 dei 29 episodi, i pazienti sono deceduti prima che fossero disponibili i risultati microbiologici. Il trattamento con colistina è stato iniziato per 11 dei 29 episodi; tre pazienti hanno ricevuto colistina in associazione a sulbactam o betalattamici in associazione a sulbactam mentre i rimanenti otto pazienti che hanno ricevuto colistina in monoterapia erano già in terapia con carbapenemi. Le infezioni da XDRAB possono facilmente trasformarsi in un incubo per i reparti di ematologia, senza la possibilità di poter contare su una opzione terapeutica affidabile.*

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