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Incidence, risk factors and outcome of multi-drug resistant *Acinetobacter baumannii* nosocomial infections during an outbreak in a burn unit

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ABSTRACT

Background: Multidrug-Resistant *Acinetobacter baumannii* (MR-AB) can cause outbreaks in burn units. We aimed to study the incidence, risk factors and outcome of MR-AB infections in a burn unit (BU).
Methods: A prospective study was conducted from April to November, 2014 during an outbreak in a BU in Paris. Weekly surveillance cultures were performed to determine MR-AB colonization. MR-AB nosocomial infections, discharge or death without MR-AB infection were considered as competing events. To identify risk factors for MR-AB infection, baseline characteristics and time-dependent variables were investigated in univariate analyses using Cox models.
Results: Eighty-six patients admissions were analyzed during the study period. Among them, 15 (17%) acquired MR-AB nosocomial infection. Median time to infection was 22 days (interquartile range: 10–26 days). Cumulative incidence of MR-AB infections was 15% at 28 days (95% CI = 8–24). Risk factors for MR-AB infection in univariate analysis were SAPS II (Hazard Ratio (HR):1.08; 95% CI:1.05–1.12; $P < 0.0001$) and ABSI (Abbreviated Burn Severity Index) scores (HR:1.32; 95% CI:1.12–1.56; $P = 0.001$), MR-AB colonization (HR:10.2; 95%CI:2.05–50.3; $P = 0.004$), invasive procedures (ventilation, arterial and/or venous catheter) ($P = 0.0001$) and $\geq$2 skin grafts (HR:10.2; 95% CI:1.76–59.6; $P = 0.010$). MR-AB infection was associated with an increased risk of death (HR: 7.11; 95%CI: 1.52–33.2; $P = 0.013$) and longer hospital stay with a median estimated increase of 10 days (IQR: 6; 14).
Conclusions: Incidence of MR-AB nosocomial infection was high during this outbreak, and was associated with prolonged hospitalization and increased risk of death. High patient severity scores, prior MR-AB colonization, invasive procedures and repeated skin grafts were associated with an increased risk of nosocomial infection.

Introduction

In recent years, multidrug-resistant *Acinetobacter baumannii* (MR-AB), defined as strains resistant to 3 or more classes of antibiotics including carbapenem, has emerged as a major cause of health care-associated infection (Fournier and Richet, 2006; Peleg et al., 2008; Munoz-Price and Weinstein, 2008; Van Looveren et al., 2004). Patients with impaired host defenses, such as intensive care units and burned patients, are particularly exposed because of the loss of their protective skin and mucosal barrier (Wong et al., 2002; Herruzo et al., 2004). In addition, due to its ability to survive on patients' skin and environmental surfaces, MR-AB is known to promote epidemic spread and nosocomial transmission (Jawad et al., 1998; Landelle et al., 2013; Kramer et al., 2006). Therefore,

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introduction of AB strains in a facility has an important potential for outbreaks and closure of hospital units can be necessary to stop epidemics (Landelle et al., 2013; Simor et al., 2002; Zanetti et al., 2007).

MR-AB infections are difficult to treat and associated with high mortality and morbidity, and longer hospital stays (Magill et al., 2014; Center for Disease Control and Prevention, 2013). Therefore, identifying risk factors for these nosocomial infections is needed to help reduce their occurrence.

The aim of this study was to evaluate prospectively the incidence, risk factors and outcome of MR-AB infections in a Burn Unit (BU) during an outbreak leading to the temporary closure of the unit.

Material and methods

Study population

A prospective single-center study was conducted in a BU located in a 600-bed public teaching hospital in Paris, France. The BU is a 15-beds unit with a multidisciplinary team of physicians and nurses (plastic surgery, intensive care). About 250 patients are admitted every year with a hospital stay of 22 days on average.

An outbreak of MR-AB was identified in the BU in January 2014. Hygienic measures were implemented to try to control the epidemic: standard hygiene measures (hand hygiene, use of gloves and coats when appropriate) and environmental cleaning of rooms before admitting a new patient. These measures were unable to control the outbreak and the unit was finally closed temporarily on November 4, 2014.

During the course of this epidemic, we implemented a prospective study to assess the incidence and risk factors for MR-AB colonization and infection, and their impact on patients' outcome. The results of the analysis regarding patient colonization have already been reported (Munier et al., 2017). Briefly, we included all consecutive patients admitted for more than 24 h to the BU from April 14 to November 4, 2014. Only the first admission for each patient was analyzed.

To identify risk factors for MR-AB infection, patient data were recorded at baseline and daily during follow-up. Baseline patient characteristics collected at admission were: age, gender, comorbidities (including diabetes mellitus, cancer/hematologic malignancies, chronic pulmonary disease, chronic heart failure, psychiatric disorder, HIV infection, obesity), admission mode (community or hospital), severity of injury evaluated by SAPS II (Simplified Acute Physiology Score II) and ABSI (Abbreviated Burn Severity Index) scores (Le Gall et al., 1993; Tobiasen et al., 1982), prior antibiotic use within 7 days prior to admission. Time dependent characteristics were prospectively collected: invasive procedures (ventilation, central venous and artery catheter, urinary catheter), antimicrobial therapy during hospitalization, number of skin grafts, and MR-AB colonization using surveillance cultures.

MR-AB infections were defined using the CDC definition for nosocomial infections and combined specific clinical findings and results of laboratory tests (Garner et al., 1988). A patient was diagnosed with MR-AB infection if he presented clinical signs of sepsis, clinical or radiological focal signs of infection with isolation of MR-AB, leading the physician to start antimicrobial therapy. These diagnoses were ascertained by two infectious disease specialists. Patients were followed in the BU until their discharge or death. The length of stay in the BU was assessed for each patient.

Microbiology

All patients admitted to BU were screened for colonization with carbapenem-resistant Gram-negative bacilli, including MR-AB. Surveillance cultures were performed at admission and weekly thereafter throughout BU stay. Surveillance cultures included inguinal skin and rectal swabs. Additional cultures were performed on burns at each dressing, on lower respiratory samples if the patient was mechanically ventilated and when infection signs or a systemic inflammatory response syndrome occurred.

Surveillance culture samples were plated on Drigalski agar with a 10-μg ertapenem disk (Biomérieux, Marcy l'Etoile, France) for inguinal and rectal swabs or on non-selective agar for burn and respiratory samples and incubated overnight at 37 °C. Colonies were selected based on color and morphology and final identification was performed using mass spectrometry (Vitek MS, Biomérieux, Marcy l'Etoile, France). Antibiotic susceptibility pattern was determined by disk diffusion method according to the CA-SFM cut-offs (Comité de l'Antibiogramme de la Société Française de Microbiologie) (CASFM, 2013).

When infection was suspected, clinical samples were studied using an appropriate method. When AB was isolated from blood cultures or clinical specimens, antibiotic susceptibility pattern was determined as described above.

Statistical analysis

Quantitative variables are presented with the median (interquartile range (IQR)); qualitative variables with counts (percentage). Risk factors of MR-AB infection were investigated among all patients enrolled in the study. A time-to-event analysis was performed, in a competing risks framework, with MR-AB infection, death or discharge without infection as competing events (Wolkewitz et al., 2008; Beyersmann et al., 2006a). Such a methodology allows accounting for the time-dependency of some potential risk factors for infection (e.g. ventilation, antibiotics prescription). Time to event was defined as the time difference between the date of admission and the date of diagnosis of infection or the date of death/discharge, whichever occurred first. Time independent variables were recorded on admission as described above. Time-dependent explanatory variables were longitudinal exposures prospectively collected as described above. Cumulative incidences of infection, death or discharge over time were estimated. Cause-specific hazard ratios (CSHR) for candidate associated factors were estimated in Cox models in univariate analysis. Given the limited number of infection events, we did not perform a multivariable analysis. The proportional hazards assumption was assessed by examination of the Schoenfeld's residuals; log-linearity assumption for continuous variables was assessed. MR-AB infection effect on survival was also estimated in a Cox model, with discharge alive as a competing event to death in the ICU. The difference in length of stay due to infection was estimated in a multistate model framework (Beyersmann et al., 2006b; Allignol et al., 2010).

All tests were two-sided and p-values lower than 0.05 were considered as indicating significant associations. Analyses were performed using R statistical platform, version 3.4.1, using the survival (Survival Analysis), cmprsk (Subdistribution Analysis of Competing Risks) and etm (Empirical Transition Matrix) packages (https://cran.r-project.org/).

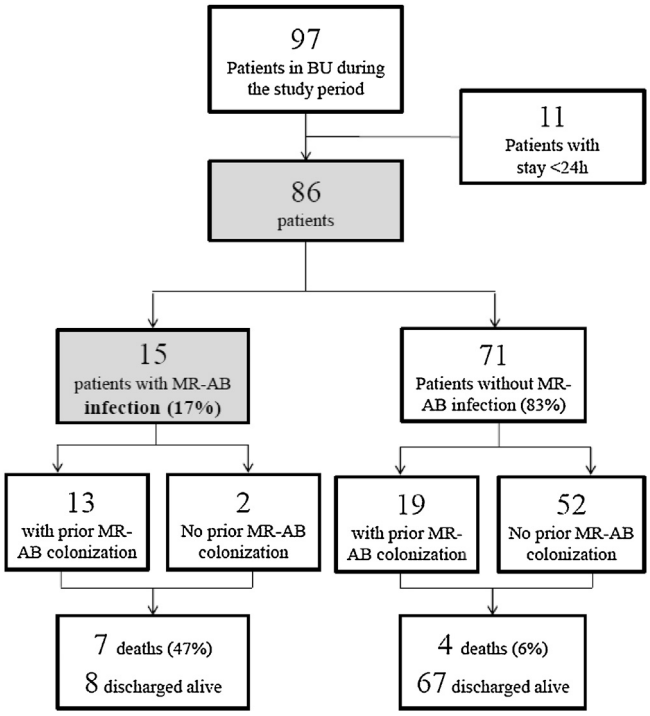

Figure 1. Study flow chart.
BU: Burn Unit.
MR-AB: Multi-Resistant *Acinetobacter baumannii*.

Results

Incidence and characteristics of nosocomial infections

From 14 April to 4 November 2014, 97 consecutive patients were admitted to BU with a total of 103 admissions (Figure 1). Eleven patients with BU length of stay of less than 24 h were excluded from the study and 86 patient admissions were included in the final analysis, representing 2492 patients-days of hospitalization. Median length of stay in the BU was 22 days (min–max: 2–105).

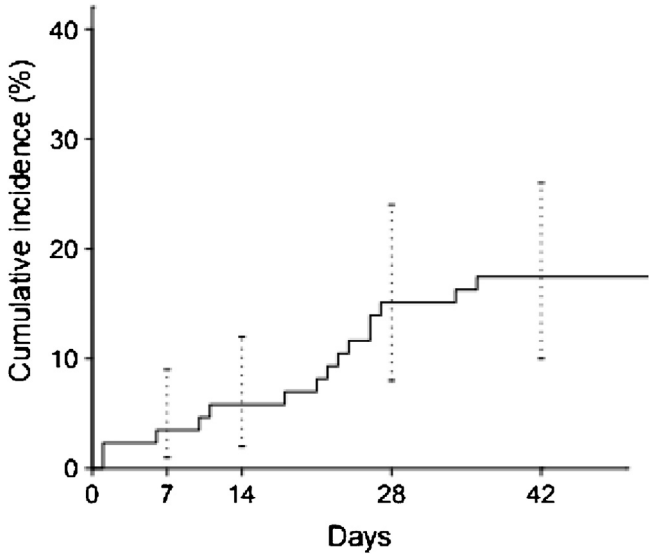

Figure 2. Cumulative incidence of MR-AB infections during hospitalization. (Vertical segments represent 95% confidence intervals of the cumulative incidence at 7, 14, 28 and 42 days).

Among these 86 admissions, 15 (17%) led to the development of a MR-AB infection. The cumulative incidence of MR-AB infection was 6% at 14 days (95% CI 2–12%), and 15% at 28 days (95% CI 8-24%) (Figure 2). Among 32 patients with MR-AB colonization, 13 (41%) developed MR-AB infection. The cumulative incidence of MR-AB infection among MR-AB colonized patients was 44% at 28 days (95% CI 27–60%) (Data not shown).

The median time from admission to onset of infection was 22 days (IQR: 10–26).

Characteristics of patients with MR-AB nosocomial infections are described in Table 1. Patients presented bloodstream infection (n = 9), pneumonia (n = 7) in ventilated patients (n = 5) or non-ventilated patients (n = 2), burn infection (n = 3), catheter-related infection (n = 3), peritonitis (n = 2), bone and joint infection (n = 1), bronchitis (n = 1). Eight patients had more than one infected site.

Of the 15 patients with clinical infection, 13 (87%) had prior documented positive surveillance culture, with a median time between positive surveillance culture and infection of 7 days (IQR 3–15). Of the 2 patients without MR-AB colonization at the time of infection, the first patient acquired infection 34 days after admission and had undergone negative surveillance cultures on 21 different days. The second patient acquired infection 5 days after admission and had undergone negative surveillance cultures on 2 different days. Median time between the last negative surveillance culture and infection was 48 h (24–72 h) in these two patients.

Risk factors of MR-AB infections

Univariate analysis of baseline and time-dependent factors associated with MR-AB infection are presented in Table 2. Risk factors of MR-AB infection were SAPS II (CSHR:1.08; 95% CI:1.05–1.12; P < 0.0001) and ABSI scores (CSHR:1.32; 95% CI:1.12–1.56; P = 0.001), MR-AB colonization (CSHR:10.2; 95%CI:2.05–50.3; P = 0.004), invasive procedures (P = 0.0001), ventilation (CSHR: 9.69; 95%CI = 3.06–30.7; P = 0.0001), artery and/or venous catheter (P < 0.0001), and ≥2 skin grafts (CSHR:10.2; 95% CI:1.76–59.6; P = 0.010).

Risk factors of MR-AB infection among MR-AB colonized patients in univariate analysis were SAPS II (CSHR = 1.06; 95% CI = 1.03–1.09; *P* = 0.0003) and invasive procedures (*P* < 0.019), particularly ventilation ≥1 day and catheter.

Outcome

The median duration of hospitalization, according to MR-AB infection and outcome (death or alive) is presented in Table 3. MR-AB infection was associated with a longer hospital stay whether patients died during hospitalization or were discharged alive. Indeed, probability of being discharged alive the next day was significantly reduced when MR-AB infected (CSHR for discharge = 0.17; 95%CI 0.06–0.49, P = 0.001), with a median estimated increase of 10 days (IQR: 6; 14) following infection.

Considering only patients who were discharged alive, median duration of hospitalization was 67 days among the 15 patients who acquired MR-AB infection and 19 days among non-infected patients.

Eleven patients (13%) died during hospitalization in the BU. Cumulative incidence of death was 6% at 28 days. MR-AB infection was associated with an increased risk of death (CSHR: 7.11; 95%CI: 1.52–33.2; P = 0.013). Seven of the 15 (46.7%) patients who acquired MR-AB infection died in the BU, after a median of 14 days (range: 5–76 days) following diagnosis. Death was related to infection in 4/7 patients (57%), uncertainly related to infection in 2 (29%) and unrelated to infection in 1 (14%).

Table 1
Characteristics and outcome of MR-AB infections.

Patient	Age	Sex	Infection	MR-AB isolation	Delay after admission	Treatment of MR-AB infection episode	Duration of treatment	Outcome	Time btw infection and death	Death related to infection
1	66	H	VAP	Tracheal aspiration	10	Colimycin + aminosides + colimycin aerosols	9	Discharge alive	–	
2	34	H	CRI + VAP	Blood culture + tracheal aspiration	25	Colimycin + colimycin aerosols	8	Discharge alive	–	
3	58	H	BSI + ventilator-associated bronchitis	Blood culture + tracheal aspiration	21	Colimycin aerosols + aminosides	5	Discharge alive	–	
4	41	H	BSI + burn infection	Blood culture + cutaneous sample	17	Colimycin + colimycin aerosols	14	Discharge alive	–	
5	56	F	CRI	Blood culture	35	Colimycin	8	Discharge alive	–	
6	17	F	CRI	Blood culture + catheter	20	Colimycin	8	Discharge alive	–	
7	73	H	BSI	Blood culture	23	Colimycin	31	Discharge alive	–	
8	56	F	Pneumonia + BJI + BSI	Blood culture + tracheal aspiration + bone sample	33	Colimycin + colimycin aerosols	11	Death	11	Yes
9	39	H	BSI + burn infection	Blood culture + cutaneous sample	5	Colimycin + aminosides + colimycin aerosols	22	Death	76	
			2nd episode peritonitis	Peritoneal fluid	58	Colimycin + colimycin aerosols	12		23	Uncertain
10	28	H	BSI + burn infection	Blood culture + cutaneous sample	26	Colimycin + aminosides + colimycin aerosols	12	Death	12	Yes
11	54	F	BSI + VAP	Blood culture + tracheal aspiration	22	Colimycin + aminosides + colimycin aerosols	16	Death	16	Yes
12	51	F	BSI + VAP + peritonitis	Blood culture + tracheal aspiration + peritoneal fluid	25	Colimycin + colimycin aerosols	6	Death	6	Yes
13	67	H	Pneumonia	Tracheal aspiration	9	Colimycin + aminosides + colimycin aerosols	6	Death	14	Uncertain
14	62	H	VAP	Distal pulmonary sample	0	Colimycin + colimycin aerosols	11	Death	20	No
15	30	H	BSI	Blood culture	0	Colimycin	8	Discharge alive	–	

CRI: catheter-related infection.
VAP: Ventilator-associated pneumonia.
BSI: Bloodstream infection.
BJI: Bone and joint infection.

Discussion

In this prospective study conducted in a BU during an outbreak of MR-AB, the incidence of MR-AB nosocomial infection was high, 15% at 28 days, and increased to 44% at 28 days among patients with prior colonization (13 of 15 patients (86.6%) with nosocomial infection had prior colonization) (Figure 2). Such a high incidence of MR-AB infection despite the implementation of infection control strategies in the BU led to its closure to allow thorough cleaning and hydrogen peroxide disinfection (Zanetti et al., 2007). A similar incidence of infection (16.5%) was reported by Latibeaudière et al. during an epidemic, and MR-AB colonization was also found in a high proportion (56.7%) of MR-AB infected patients (Latibeaudiere et al., 2015).

In our study, MR-AB nosocomial infections were associated with a prolonged hospitalization with a median increase of 10 days following infection, similar to previous reports (Wong et al., 2002).

Also, among patients who acquired MR-AB infection, 7/15 (46.7%) died as compared to 4/71 (5.6%) without infection (Figure 1). In our study, MR-AB infections were associated with a significant increase in the risk of death (CSHR: 7.11; 95%CI: 1.52–33.2; P = 0.013). Wong et al. did not find in a retrospective study among patients in a burn unit in Singapore that MR-AB infection was associated to an increased mortality (Wong et al., 2002). Wisplinghoff et al. reported that the mortality rate in MR-AB infected patients was twice higher than in controls in a retrospective case control study in Germany (Wisplinghoff et al., 1999). Our results obtained in the setting of a prospective study strengthen the association between MR-AB and increased risk for death, even though we cannot ascertain in all our cases that death was directly related to MR-AB infection. Death was directly related to infection in 4/7 (57%) of MR-AB infected patients who died.

Bloodstream infection and pulmonary infections were the most frequent infections and 12/15 (80%) patients with nosocomial infection had positive blood cultures (Table 1). This high death rate in our study is probably related in part to the severity of the patients, the dissemination of the infection, and the limited efficacy of antibiotic therapy against these multi-resistant organisms.

It is therefore critical to analyze in such a study risk factors for nosocomial infections in order to try to prevent or diagnose and

Table 2
Characteristics of patients and univariate analysis of the association with MR-AB infection, estimated using cause specific hazard ratios (CSHR).

Variables	All patients n = 86	No MR-AB infection n = 71 (83)	MR-AB infection n = 15 (17)	Univariate analysis	
				CSHR (95% CI)	P value
Baseline characteristics					
Median age, y	46 (30; 58)	46 (30; 58)	53 (36; 60)	1.00 (0.98; 1.03)	0.75
Male gender	53 (62)	43 (61)	10 (67)	1.55 (0.53; 4.57)	0.43
At least 1 comorbidity	34 (40)	24 (34)	10 (67)	2.25 (0.77; 6.62)	0.14
Diabetes	8 (9)	7 (10)	1 (7)		
Cancer	4 (5)	2 (3)	2 (13)		
Chronic pulmonary disease	3 (3)	1 (1)	2 (13)		
Chronic heart failure	3 (3)	2 (3)	1 (7)		
Psychiatric disorder	18 (21)	11 (15)	7 (47)		
HIV infection	1 (1)	1 (1)	0 (0)		
Obesity	4 (5)	3 (4)	1 (7)		
Admission mode					
Community	58 (67)	47 (66)	11 (73)		
Hospital	28 (33)	24 (34)	4 (27)	0.64 (0.20; 2.01)	0.44
Median SAPS II	20 (15: 32)	17 (12; 24)	41 (27; 50)	**1.08 (1.05; 1.12)**	**<0.0001**
Median ABSI[a]	6 (5; 8)	6 (5; 7)	9 (7; 10)	**1.32 (1.12; 1.56)**	**0.001**
Prior antibiotic use (within 7 days)	21 (24)	16 (23)	5 (33)	1.34 (0.46; 3.93)	0.59
MR-AB colonization on admission	9 (10)	5 (7)	4 (27)		
Time-dependent characteristics[b]					
MR-AB colonization (previous day)	32 (37)	19 (27)	13 (87)	**10.2 (2.05; 50.3)**	**0.004**
Invasive procedure (≥1 day)	65 (76)	50 (70)	15 (100)	–	**0.001***
Ventilation (≥1 day)	31 (36)	18 (25)	13 (87)	**9.69 (3.06; 30.7)**	**0.0001**
Catheter	48 (56)	33 (46)	15 (100)	–	**<0.0001***
≥2 skin grafts during the stay[c]	25 (29)	14 (20)	11 (73)	**10.2 (1.76; 59.6)**	**0.01**
Antibiotic treatment ≥1 day[d]	39 (45)	27 (38)	12 (80)	6.04 (0.76; 48.3)	0.09

Data are presented as No. (%) unless otherwise specified.
[a] Estimations among burn patients only (n = 68).
[b] Exposure to time dependent characteristics estimated from admission to first outcome (colonization, death or discharge alive).
[c] CSHR for ≥2 skin grafts vs <2 skin grafts (reference).
[d] ≥1 day of antibiotics; duration is reported in days, with median (interquartile range).
* All infections occurred in patients with exposure (invasive procedures and catheter respectively). CSHRs had infinite values; P-values correspond to the score test in a Cox regression model.

Table 3
Median length (min; max) of hospital stays in days according to MR-AB infection and outcome (death or discharged alive).

End of stay status	All N = 86	No MR-AB infection N = 71	MR-AB infection N = 15
Death	31 (3; 82)	8.5 (3; 43)	39 (21; 82)
Discharge alive	21 (2; 105)	19 (2; 76)	67 (9; 105)

treat as early as possible these infections, until the outbreak is under control.

Due to the limited number of cases (Harrell, 2015), we could only perform a univariate analysis of risk factors associated with MR-AB infections and this is a clear limitation of our findings. We found that the severity of patients at admission as measured by the SAPS II and ABSI scores, prior colonization by MR-AB, invasive procedures during hospitalization (ventilation, venous or arterial catheter), and 2 or more skin grafts were strongly associated with an increased risk of infection (Table 2). In an exploratory analysis that should be interpreted and generalized with caution (Harrell, 2015), we found that prior colonization by MR-AB remained significantly associated with MR-AB infection (HR = 5.95, 95%CI 1.11–31.9, P = 0.037), when adjusted in ABSI scores to account for illness severity. Similarly, MR-AB infection association with ICU death remained close to the 5%-significance level after adjustment on ABSI score (HR = 5.84, 95%CI 0.96; 1.56, P = 0.056).

Our results confirm the results of previous studies in intensive care units that have identified the severity of illness/comorbidity, invasive procedures, mechanical ventilation, long duration of hospital stay (Garnacho-Montero et al., 2005; Baran et al., 2008), and the role of prior MR-AB colonization (Latibeaudiere et al., 2015; Playford et al., 2007). Our study however, is the first prospective study assessing risk factors of MR-AB infection in a burn unit.

Contrary to previous reports, prior exposure to antimicrobials was not a risk factor for infection in our study but was associated with an increased risk of colonization (Zanetti et al., 2007; Garnacho-Montero et al., 2005). A previous study conducted in Brazil, where MR-AB colonization is endemic, found that use of antimicrobials was a risk factor for acquisition of MR-AB only when colonization pressure (proportion of patients harboring the microorganism) was low (Castelo Branco Fortaleza et al., 2013). Thus, the absence of association between antimicrobials and MDR-AB infection could be explained either by low sensitivity of analysis (due to small number of infection events) or by high colonization pressure during the outbreak.

However, the role of prior colonization leading to infection is reinforced in our prospective study since 13/15 (87%) patients with infections had prior colonization, and the CSHR for infection in colonized patients was significantly greater than 1 (10.2; 95%CI: 2.05–50.3; P = 0.004). Latibeaudiere et al. in their retrospective studies have previously reported that positive surveillance cultures were the only variable associated with infection in a multivariate analysis (Latibeaudiere et al., 2015). The role of these surveillance cultures during an outbreak is therefore critical to identify early colonization and patients at high risk for these life-threatening infections. Nineteen MR-AB colonized patients did not develop an infection. These patients were less severe patients with fewer invasive devices as compared to MR-AB colonized patients who develop a MR-AB infection. Once a patient is colonized, the

reduction in invasive procedures may limit the risk of transition from colonization to infection. However, this is difficult to apply in severe burn patients.

Another risk factor for infection in our study in a BU was the number of skin grafts. Indeed patients who underwent 2 or more skin grafts had a higher risk of MR-AB infection (CSHR: 10.2; 95% CI:1.76–59.6; P = 0.010). This risk factor has not been previously reported to be associated with an increased risk of MR-AB infection. The number of skin grafts needed in a burned patient is clearly linked to the severity of burns as measured by the ABSI score. In our univariate analysis, it is therefore difficult to know whether the number of skin grafts is a confounding factor, a proxy of burn severity, and further studies should try to address this issue.

In conclusion, this prospective study found a very high incidence of MR-AB nosocomial infection during an outbreak in a BU, associated with prolonged hospitalization and increased risk for death in those infected. Surveillance cultures should be performed to identify colonized patients in whom the risk of MR-AB infection is greatly increased, especially in those with a severe injury as assessed by SAPS II and ABSI scores, those undergoing multiple skin grafts, or various invasive procedures. As it seems difficult to limit the number of skin grafts or invasive procedures needed to manage severely burned patients, prevention of MR-AB colonization remains critical. As reported earlier, since the use of antibiotic therapy is strongly associated with colonization (Munier et al., 2017), its use should therefore be limited as much as possible during an outbreak.

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Compliance with ethical standards

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All authors declare they have no conflict of interest.

The ethical committee of the hospital deemed specific approval for this study unnecessary.

Not applicable (as discussed with the institutional medical ethical committee).

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