Hetero- and adaptive resistance to polymyxin B in OXA-23-producing carbapenem-resistant Acinetobacter baumannii isolates

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Abstract

Background: Resistance rates to polymyxin B in surveillance studies have been very low despite its increasing use worldwide as the last resort therapy for multidrug-resistant Gram-negative bacilli. However, two other resistance phenotypes, hetero- and adaptive resistance, have been reported to polymyxin. We aimed to investigate the presence of polymyxin B hetero- and adaptive resistance and evaluate its stability in carbapenem-resistant Acinetobacter baumannii (CRAB) clinical isolates.

Methods: CRAB isolates were recovered from hospitalized patients at three Brazilian hospitals. Hetero-resistance was determined by population analysis profile (PAP). Adaptive resistance was evaluated after serial daily passages of isolates in Luria-Bertani broth containing increasing polymyxin B concentrations. MICs of polymyxin B of colonies growing at the highest polymyxin B concentration were further determined after daily sub-cultured in antibiotic-free medium and after storage at −80°C, in some selected isolates.

Results: Eighty OXA-23-producing CRAB isolates were typed resulting in 15 distinct clones. Twenty-nine randomly selected isolates (at least one from each clone) were selected for hetero- resistance evaluation: 26 (90%) presented growth of subpopulations with higher polymyxin B MIC than the original one in PAP. No isolate has grown at polymyxin B concentrations higher than 2 mg/L. Polymyxin B MICs of subpopulations remained higher than the original population after daily passages on antibiotic-free medium but returned to the same or similar levels after storage. Twenty-two of the 29 isolates (at least one from each clone) were evaluated for adaptive resistance: 12 (55%) presented growth in plates containing 64 mg/L of polymyxin B. Polymyxin B MICs decreased after daily passages on antibiotic-free medium and returned to the same levels after storage.

Conclusions: The presence of subpopulations with higher polymyxin B MIC was extremely common and high-level adaptive resistance was very frequent in CRAB isolates.

Keywords: Acinetobacter baumannii, Polymyxins, Polymyxin B, Colistin, Hetero-resistance, Adaptive resistance, Multidrug-resistance, Carbapenemase
Background
The increasing worldwide prevalence of multi-drug resistant, *Acinetobacter baumannii*, a major nosocomial pathogen, particularly carbapenem-resistant strains, is of great concern, since treatment becomes restricted to very few options [1]. Polymyxins, both B and E (colistin), are “old” polypeptide antibiotics that re-emerged in clinical practice as the last resort therapy against multidrug-resistant Gram-negative bacteria; many, including *A. baumannii*, are only susceptible to these drugs [2]. Although resistance rates to polymyxins in surveillance studies fortunately remain very low [3], two relatively poorly understood resistance phenotypes, hetero- and adaptive resistance, have been reported in these drugs [4,5].

The term hetero-resistance refers to a phenotype characterized by the presence of different (drug-resistant and –susceptible) populations in a single clinical specimen or isolate [6], while adaptive resistance describes an autoregulated phenomenon characterized by rapid induction of resistance in the presence of drug and reversal to the susceptible phenotype in its absence [7].

Hetero-resistance has been recently described for colistin in some carbapenem-resistant *A. baumannii*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* isolates [8-10], and other studies have demonstrated the presence of adaptive resistance to polymyxins, mainly in *P. aeruginosa* [7]. No study so far has neither investigated the presence of hetero-resistance for polymyxin B, the frequency of adaptive resistance in carbapenem-resistant *A. baumannii* (CRAB) isolates, nor assessed the presence of these distinct phenomena in the same isolates. The aim of this study was to assess the occurrence of these phenomena and evaluate its stability in CRAB clinical isolates.

Methods

**Bacterial strains**
CRAB isolates were selected from a total of 132 *Acinetobacter* spp. isolates (one isolate by patient) consecutively recovered from patients admitted to three tertiary-care hospitals from Porto Alegre, Brazil, from March to December 2011. Isolates were identified by Vitek 2 system. The following carbapenemase-encoding genes were examined by multiplex PCR: blaOXA-23, blaOXA-24, blaOXA-51, blaOXA-58 and blaOXA-143 genes [11]. *A. baumannii* species was confirmed by the presence of the intrinsic blaOXA-51 gene [12].

MICs for polymyxin B, imipenem and meropenem were determined by broth microdilution and interpreted according to CLSI guidelines [13]. *Pseudomonas aeruginosa* ATCC 27853 was included as quality control in all tests.

CRAB isolates were submitted to molecular typing by ApaI DNA macrorestriction followed by PFGE [14]. Results were interpreted using a dendrogram constructed using the band-based Dice coefficient method, and, for the purpose of this study, isolates with >90% were considered a clone.

**Hetero-resistance**

Hetero-resistance in selected CRAB isolates was determined by population analysis profile (PAP). Briefly, solutions containing seven distinct bacterial inoculum, ranging from 10⁸ (0.5 McFarland standard) to 10² CFU/ml were prepared to facilitate bacterial counting in each plate. A 20 μL aliquot of each solution was spread on Mueller-Hinton agar plates containing 0, 0.5, 1, 2, 3, 4 and 6 mg/L of polymyxin B. Colonies were counted after 48 h of incubation at 35°C. The limit of counting was 20 CFU/ml. The frequency of hetero-resistant subpopulations at the highest drug concentration was calculated by dividing the number of colonies grown on antibiotic-containing plates by the colony counts from the same bacterial inoculum plated onto antibiotic-free plates [9]. MICs of polymyxin B of these subpopulations growing at the highest polymyxin B concentration were determined after daily sub-cultured in antibiotic-free medium for 4 days and after 75 days storage at ~80°C, in some selected isolates.

**Adaptive resistance**

Isolates were submitted to serial daily passages in freshly prepared Luria-Bertani (LB) broth containing increasing polymyxin B concentrations of 0.25 to 64 mg/L for a total of nine days (adapted from Fernandez et al. [15]). MICs of polymyxin B of colonies growing at the highest polymyxin B concentration were also determined after daily subculture in antibiotic-free medium for 3 days and after 60 days storage at ~80°C, in some isolates.

Results

Of the 132 *Acinetobacter* spp., 124 were confirmed as *A. baumannii* by the presence of blaOXA-51 gene, and 89 (71.7%) of these were CRAB isolates. All CRAB isolates were positive for blaOXA-23 and no product of amplification was detected for the other carbapenemase-encoding genes. Of these, 80 were typed, resulting in 15 distinct clones. MIC50 for both imipenem and meropenem were 64 mg/L and 32 mg/L and MIC90 were 128 mg/L and 64 mg/L, respectively. MIC of polymyxin B ranged from ≤0.125 mg/L to ≥64 mg/L. Twenty-nine randomly selected isolates (at least one from each clone) were selected for hetero-resistance evaluation.

PAP revealed the growth of subpopulation with 2- to at least 4 fold dilutions higher polymyxin B MIC than the original population in 26 (90%) of 29 isolates, including at least one isolate representative of each clone (Table 1). No isolate has grown at polymyxin B concentrations higher than 2 mg/L. The proportions of higher MIC
subpopulations ranged from $2.5 \times 10^{-7}$ to $6.2 \times 10^{-4}$. MICs of polymyxin B of the 26 “higher MIC” subpopulations remained higher than the original population MIC after daily passages on polymyxin B-free medium (Table 1). After storage, MIC for polymyxin B among 17 selected subpopulations with higher MIC returned to levels similar to the original population, with most presenting exactly the same MIC of the original population.

Twenty-two of the 29 isolate (at least one from each clone) were evaluated for adaptive resistance. In twelve isolates, growth was observed in plates containing 64 mg/L of polymyxin B (Table 2). After daily passages on polymyxin B-free medium for 3 days the MIC of isolates growing at 64 mg/L remained the same for two isolates and decreased 1- to 2-fold dilutions for the other ten (Table 2). Polymyxin B MICs after 60 day storage (performed in four isolates) were exactly the same of the MIC of baseline.

**Discussion**

Our study for the first time investigated the presence of hetero- and adaptive resistance to polymyxin B in unrelated OXA-23-producing CRAB isolates. Additionally, the stability of these phenomena was evaluated in two distinct conditions. Since the susceptibility breakpoint for polymyxin B according to CLSI is 2 mg/L [13], real hetero-resistance for polymyxin B was not found in any isolate, differently from previous studies with colistin [9,16,17]. However, the presence of “higher MIC” subpopulations, within the susceptibility range, was detected in 90% of tested isolates, including at least one

Table 1 Results of population analysis profile (PAP) of selected carbapenem-resistant *Acinetobacter baumannii* isolates

| Strain | PFGE group | MIC (mg/L) | Frequency of appearance of subpopulations (PAP) | MIC after 4 days daily passages in drug-free medium (mg/L) | MIC after 75 days storage (mg/L) |
|--------|------------|------------|------------------------------------------------|--------------------------------------------------|---------------------------------|
| 1      | A          | $\leq 0.125$ | 1                                               | $6.6 \times 10^{-5}$                          | $\leq 0.125$                     |
| 2      | A          | $\leq 0.125$ | 2                                               | $6 \times 10^{-5}$                           | $\leq 0.125$                     |
| 3      | A          | 0.25        | NG                                              | NA                                              | NA                              |
| 4      | A          | $\leq 0.125$ | 1                                               | $1 \times 10^{-7}$                           | NA                              |
| 5      | A          | 0.25        | 1                                               | $5 \times 10^{-5}$                           | NP                              |
| 6      | A          | 0.25        | 1                                               | $1.5 \times 10^{-6}$                          | NP                              |
| 7      | B          | $\leq 0.125$ | 0.5                                            | $5 \times 10^{-4}$                           | $0.5 \leq 0.125$                |
| 8      | B          | 0.25        | 1                                               | $2.5 \times 10^{-7}$                          | 0.25                            |
| 9      | B          | $\leq 0.125$ | 0.5                                            | $1 \times 10^{-6}$                           | NP                              |
| 10     | C          | $\leq 0.125$ | 1                                               | $1.2 \times 10^{-5}$                          | $\leq 0.125$                     |
| 11     | C          | 1           | 1                                               | NA                                              | 1                               |
| 12     | C          | $\leq 0.125$ | 1                                               | $7.1 \times 10^{-5}$                          | NP                              |
| 13     | D          | $\leq 0.125$ | 1                                               | $1.3 \times 10^{-6}$                          | NP                              |
| 14     | D          | $\leq 0.125$ | 1                                               | $3.3 \times 10^{-6}$                          | NP                              |
| 15     | E          | 0.25        | 1                                               | $1 \times 10^{-6}$                           | NP                              |
| 16     | F          | 0.5         | 2                                               | $8.3 \times 10^{-5}$                          | 1                               |
| 17     | F          | $\leq 0.125$ | 1                                               | $1 \times 10^{-6}$                           | $\leq 0.125$                     |
| 18     | G          | 0.25        | 1                                               | $7.5 \times 10^{-5}$                          | 0.25                            |
| 19     | H          | 0.25        | 1                                               | $3.3 \times 10^{-4}$                          | 0.25                            |
| 20     | I          | 0.25        | 2                                               | $3.3 \times 10^{-5}$                          | 1                               |
| 21     | I          | 0.5         | 1                                               | $3 \times 10^{-6}$                            | 1                               |
| 22     | J          | 0.25        | 1                                               | $1.4 \times 10^{-4}$                          | 0.25                            |
| 23     | K          | 0.25        | NG                                              | NA                                              | NA                              |
| 24     | L          | $\leq 0.125$ | 0.5                                            | $1.5 \times 10^{-6}$                          | $0.5 \leq 0.125$                |
| 25     | L          | $\leq 0.125$ | 1                                               | $4 \times 10^{-4}$                           | NP                              |
| 26     | M          | $\leq 0.125$ | 1                                               | $6.2 \times 10^{-4}$                          | $\leq 0.125$                    |
| 27     | N          | 0.5         | 2                                               | $6.6 \times 10^{-5}$                          | 1                               |
| 28     | N          | $\leq 0.125$ | 0.5                                            | $1.5 \times 10^{-5}$                          | NP                              |
| 29     | O          | $\leq 0.125$ | 1                                               | $5 \times 10^{-5}$                           | 0.5                             |

PAPs population analysis profiles, NA not applicable, NG no growth, NP not performed.
isolate representative of each of the 15 clones. These 
“higher MIC” subpopulations presented MICs 2- to at 
least 4-fold dilutions higher than the original population.

The presence of adaptive resistance to polymyxin B 
was shown in 55% of 22 tested isolates (present in 7 of 
15 clones), all demonstrating high-level resistance to 
polymyxin B (MIC = 64 mg/L). Although some mo-
olecular mechanisms of adaptive resistance to poly-
myxins, such as mutations in pmrCAB and lpxA gene 
in A. baumannii [18,19] and PhoP-PhoQ, PmrA-PmrB 
and recently ParR-ParS in P. aeruginosa [15], have 
been characterized, the presence of this resistance 
phenotype has not been systematically evaluated. Thus, 
our study further suggests that adaptative resistance 
might be most common than possibly expected, at 
least in CRAB, since approximately half of tested 
clones showed such adaptive phenotype. Indeed, the 
frequency might be even higher if the agar plate with 
the lowest polymyxin B concentration had ≤0.25 mg/L 
of the drug. Although seven isolates with MIC ≤0.125 
mg/L still have growth on these plates, these concen-
trations may have inhibited the growth of other eight 
isolates.

The present study also showed that the MIC of the 
“higher MIC” subpopulations remained stable after 4-days 
into antimicrobial-free medium, but returns to the MIC of 
the original population after storage at −80°C, suggesting 
that it might involve some molecular basis also associated 
with an unstable phenotype. As expected, since without 
the drug-sustaining effect the adaptive resistance is 
unstable, the MICs of resistant isolates selected in the 
adaptive resistance experiment decreased 1- to 2-fold 
dilutions after serial passage into antimicrobial-free 
medium and all tested isolates returns to the baseline 
level after the storage at −80°C.

Only one isolate that has presented adaptive resistance 
has not presented “higher MIC” subpopulation in PAP. 
It belongs to the clone A, which has other three isolates 
tested in both experiments, all showing the presence of 
both phenomena. It is also interesting that these latter 
three isolates were identical by typing while the former 
showed 92% of similarity with these latter ones (data not 
shown). Another isolate has neither presented “higher 
MIC” subpopulation nor adaptive resistance and belongs 
to a clone with two representative isolates among the 80 
CRAB typed in this study.

| Strain | PFGE group | MIC (mg/L) | Polymyxin B MIC of subpopulations selected in PAP | Highest concentration of polymyxin B where growth was observed (mg/L) | MIC after 3 days daily passages in drug-free medium (mg/L) | MIC after 60 days storage (mg/L) |
|--------|------------|------------|-----------------------------------------------|----------------------------------------------------------------|-------------------------------------------------|-------------------------------|
| 2      | A          | ≤0.125     | 2                                             | 64                                                                | 32                                              | NP                            |
| 3      | A          | 0.25       | NA                                            | 64                                                                | 16                                              | NP                            |
| 5      | A          | 0.25       | 1                                             | NG                                                                | NA                                              | NA                            |
| 6      | A          | 1          | 1                                             | 64                                                                | 16                                              | NP                            |
| 7      | B          | ≤0.125     | 0.5                                           | 64                                                                | 16                                              | NP                            |
| 8      | B          | 0.25       | 1                                             | 64                                                                | 16                                              | NP                            |
| 9      | B          | ≤0.125     | 0.5                                           | 64                                                                | 16                                              | NP                            |
| 10     | C          | ≤0.125     | 1                                             | 64                                                                | 32                                              | ≤0.125                        |
| 12     | C          | ≤0.125     | 1                                             | 64                                                                | 16                                              | NP                            |
| 14     | D          | ≤0.125     | 1                                             | NG                                                                | NA                                              | NA                            |
| 15     | E          | 0.25       | 1                                             | NG                                                                | NA                                              | NA                            |
| 16     | F          | 0.5        | 2                                             | NG                                                                | NA                                              | NA                            |
| 17     | F          | ≤0.125     | 1                                             | NG                                                                | NA                                              | NA                            |
| 18     | G          | 0.25       | 1                                             | 64                                                                | ≥64                                             | NP                            |
| 19     | H          | 0.25       | 1                                             | NG                                                                | NA                                              | NA                            |
| 20     | I          | 0.25       | 2                                             | NG                                                                | NA                                              | NA                            |
| 22     | J          | 0.25       | 1                                             | 64                                                                | 16                                              | 0.25                          |
| 23     | K          | 0.25       | NA                                            | NG                                                                | NA                                              | NA                            |
| 24     | L          | ≤0.125     | 0.5                                           | 64                                                                | 16                                              | ≤0.125                        |
| 26     | M          | ≤0.125     | 1                                             | 64                                                                | ≥64                                             | ≤0.125                        |
| 27     | N          | 0.5        | 2                                             | NG                                                                | NA                                              | NA                            |
| 29     | O          | ≤0.125     | 1                                             | NG                                                                | NA                                              | NA                            |

PAP population analysis profiles, NA not applicable, NG no growth, NP not performed.

Table 2 Results of adaptive resistant experiments of selected carbapenem-resistant *Acinetobacter baumannii* isolates

The present study also showed that the MIC of the “higher MIC” subpopulations remained stable after 4-days into antimicrobial-free medium, but returns to the MIC of the original population after storage at −80°C, suggesting that it might involve some molecular basis also associated with an unstable phenotype. As expected, since without the drug-sustaining effect the adaptive resistance is unstable, the MICs of resistant isolates selected in the adaptive resistance experiment decreased 1- to 2-fold dilutions after serial passage into antimicrobial-free medium and all tested isolates returns to the baseline level after the storage at −80°C.

Only one isolate that has presented adaptive resistance has not presented “higher MIC” subpopulation in PAP. It belongs to the clone A, which has other three isolates tested in both experiments, all showing the presence of both phenomena. It is also interesting that these latter three isolates were identical by typing while the former showed 92% of similarity with these latter ones (data not shown). Another isolate has neither presented “higher MIC” subpopulation nor adaptive resistance and belongs to a clone with two representative isolates among the 80 CRAB typed in this study.
Unfortunately, we were not able to determine the molecular determinants of these phenotypes in this study. We also could not determine if the absence of real hetero-resistance (i.e. presence of subpopulations with MICs higher than the susceptibility breakpoint) was a specific characteristic of polymyxin B, and would occur with colistin, or “higher MIC” subpopulations within the susceptibility range was only detected, instead of subpopulations with “resistance MICs” because the baseline MIC of half of the tested isolates were very low (≤0.125 mg/L).

In summary, our study showed that the presence of “higher MIC” subpopulations in CRAB isolates was extremely common. Additionally, high-level adaptive resistance was also very frequent. The clinical significance of each phenomenon should be further investigated, since both may potentially affect the outcomes of patients on therapy with polymyxins.

Competing interests
APZ has received consultancy fees from Pfizer, Eurofarma and Forest Laboratories. All other authors: none to declare.

Authors’ contributions
JB was responsible for performance of the experiments, data interpretation and drafting the manuscript; BJA performed the experiments and contributed to manuscript draft; AFM and ALB contributed in the experiments, data interpretation and manuscript draft; and APZ conceived the study, contributed in data interpretation, drafting and reviewing of the manuscript. All authors read and approved the final manuscript.

Acknowledgements
This work was supported by Fundo de Incentivo à Pesquisa e Eventos do Hospital de Clínicas de Porto Alegre (12–0010) and Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (110898-3), Brazil. A. P. Z. and A.L. B. are research fellows from the National Council for Scientific and Technological Development, Ministry of Science and Technology, Brazil.

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Received: 7 March 2013 Accepted: 26 June 2013 Published: 2 July 2013

References
1. Vila J, Pachón J. Therapeutic options for Acinetobacter baumannii infections: an update. Expert Opin Pharmacother 2012, 13:2319–2336.
2. Zavarski AP, Goldani LZ, Li J, Nation RL. Polymyxin B for the treatment of multidrug-resistant pathogens: a critical review. J Antimicrob Chemother 2007, 60:1206–1215.
3. Gales AC, Jones RN, Sader HS. Contemporary activity of colistin and polymyxin B against a worldwide collection of gram-negative pathogens: results from the SENTRY antimicrobial surveillance program (2006–09). J Antimicrob Chemother 2011, 66:2070–2074.
4. Falagas ME, Rafaellidis PI, Matthaiou DK. Resistance to polymyxins: mechanisms, frequency and treatment options. Drug Resist Updat 2010, 13:132–138.
5. Cai Y, Chai D, Wang R, Liang B, Bai N. Colistin resistance of Acinetobacter baumannii: clinical reports, mechanisms and antimicrobial strategies. J Antimicrob Chemother 2012, 67:1607–1615.
6. Falagas ME, Makris GC, Dimopoulou G, Matthaiou DK. Heteroresistance: a concern of increasing clinical significance? Clin Microbiol Infect 2008, 14:101–104.
7. Skiada A, Markogiannakis A, Plachouras D, Daikos GL. Adaptive resistance to cationic compounds in Pseudomonas aeruginosa. Int J Antimicrob Agents 2011, 37:187–193.
8. Pourmaras S, Ikonomidou A, Markogiannakis A, Spanakis N, Maniatis AN, Tsakris A. Characterization of clinical isolates of Pseudomonas aeruginosa heteroresistant to carbapenems. J Med Microbiol 2007, 56:66–70.
9. You W, Owen RJ, Pouady A, Bell JM, Tumidje JD, Yu HH, Nation RL, Li J. Colistin hetero-resistance in multidrug-resistant Acinetobacter baumannii clinical isolates from the Western Pacific region in the SENTRY antimicrobial surveillance programme. J Infect 2009, 58:138–144.
10. Meletis G, Tzampaz E, Sianou E, Tzavaras I, Sofianou D. Colistin heteroresistance in carbapenemase-producing Klebsiella pneumonia. J Antimicrob Chemother 2011, 66:946–947.
11. Higgins PG, Lehmann M, seifert H. Inclusion of OXA-143 primers in a multiplex polymerase chain reaction (PCR) for genes encoding prevalent OXA carbapenemases in Acinetobacter spp. Int J Antimicrob Agents 2010, 35:305–314.
12. Turkon JF, Woodford N, Glover J, Yarde S, Kaufmann ME, Pitt TL. Identification of Acinetobacter baumannii by detection of the bldO-A5,bldA Carbenapenem gene intrinsic to this species. J Clin Microbiol 2006, 44:2974–2976.
13. Clinical and Laboratory Standards Institute (CLSI): Performance Standards for Antimicrobial Susceptibility Testing: Twenty-First Informational Supplement. Wayne, PA, USA: CLSI document M100-S21; 2011.
14. seifert H, Dolzani L, Bressan R, van der Reijden T, van Strijen B, Stefanik D, de Heersma, Dukhsaam L. Standardization and interlaboratory reproducibility assessment of pulsed-field gel electrophoresis-generated fingerprints of Acinetobacter baumannii. J Clin Microbiol 2005, 43:4328–4335.
15. Fernández L, Gooderham WJ, Bains M, McPhee JB, Wiegand I, Hancock RE. Adaptive resistance to the “Last Hope” antibiotics polymyxin B and colistin in Pseudomonas aeruginosa is mediated by the novel two-component regulatory system ParP-ParR. J Antimicrob Chemother 2010, 65:3372–3382.
16. Li J, Rayner CR, Nation RL, Owen RJ, Spelman D, Tan KE, Liolios L. Heteroresistance to colistin in multidrug-resistant Acinetobacter baumannii. Antimicrob Agents Chemother 2006, 50:2946–2950.
17. Hawley JS, Murray CK, Jørgensen JH. Colistin heteroresistance in Acinetobacter and its association with previous colistin therapy. Antimicrob Agents Chemother 2008, 52:351–352.
18. Adams MD, Nickel GC, Bajaksouzian S, Lavender H, Murthy AR, Jacobs MR, Bonomo RA. Resistance to colistin in Acinetobacter baumannii associated with mutations in the PmrAB two-component system. Antimicrob Agents Chemother 2009, 53:3628–3634.
19. Moffatt JH, Harper M, Harrison P, Hale JD, Vinogradov E, Seemann T, Henry R, Crane B, St Michael F, Cox AD, Adler B, Nation RL, Li J, Boyce JD. Colistin resistance in Acinetobacter baumannii is mediated by complete loss of lipopolysaccharide production. Antimicrob Agents Chemother 2010, 54:4971–4977.

Cite this article as: Barin et al. Hetero- and adaptive resistance to polymyxin B in OXA-23-producing colistin-resistant Acinetobacter baumannii isolates. Annals of Clinical Microbiology and Antimicrobials 2013 12:15.