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**Resistência bacteriana a antimicrobianos em uma comunidade remota da
Floresta Amazônica**

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RESUMO

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O aparecimento e a disseminação de bactérias multi-resistentes estão estreitamente relacionados ao uso excessivo e inadequado de antimicrobianos em medicina humana/veterinária e na produção animal. Entretanto, alguns estudos têm relatado a presença dessas bactérias em comunidades remotas com baixa ou mínima exposição a antimicrobianos. Assim, o objetivo deste trabalho foi investigar a presença de bactérias produtoras de β -lactamases adquiridas, mediadas por plasmídeos, na microbiota Gram-negativa comensal de humanos e animais domésticos de diferentes etnias indígenas na região da Floresta Amazônica, e elucidar o seu contexto genético. No mês de março de 2013 foram coletadas amostras de fezes de indivíduos atendidos ($n = 36$) e funcionários ($n = 9$) de um centro assistencial em saúde restrito a comunidades indígenas. Adicionalmente, no mês de julho, foram coletadas amostras de “swab” retal de animais de companhia ($n = 20$) da comunidade. A identificação das espécies bacterianas foi feita por MALDI-TOF e a avaliação da susceptibilidade aos antimicrobianos foi realizada pela técnica de Kirby-Bauer. A detecção de genes de resistência e a determinação de filogrupos de *E. coli* foi feita por PCR. A genotipagem dos isolados foi feita por ERIC-PCR e MLST. As avaliações de transferibilidade, tamanho e grupos de incompatibilidade plasmidial (Inc) foram realizadas por conjugação e transformação, S1-PFGE e PBRT, respectivamente. Isolados representativos de cada grupo clonal tiveram o genoma completo sequenciado. Surpreendentemente, foram identificados 30 isolados de origem humana e cinco de origem animal apresentando resistência a cefalosporinas e fluoroquinolonas. A presença dos genes bla_{TEM-1} (78,6%) > $bla_{CTX-M-15}$ (71,4%) > $bla_{CTX-M-14}$ (21,4%) > $bla_{CTX-M-8}$ e bla_{GES-5} (7,1% cada) foi confirmada em 14 isolados (provenientes de 10 indivíduos), sendo a maioria identificada como *E. coli* (70%). Adicionalmente, a presença dos genes $bla_{CTX-M-14}$ (60%) > bla_{TEM-1} (40%) > $bla_{CTX-M-2}$ e $bla_{CTX-M-8}$ (20% cada) foi confirmada em cinco cepas de *E. coli* isoladas de cães. O filogrupo D de *E. coli* foi predominantemente encontrado, tanto em isolados de humanos ($n = 6$) quanto de animais ($n = 4$). Foi observada relação clonal entre cinco isolados de *E. coli* de humanos e três de animais, e todos os isolados de *K. pneumoniae* foram representados por um único clone. A transferibilidade plasmidial foi observada em nove isolados carregando os genes bla_{TEM} , $bla_{CTX-M-15}$, $bla_{CTX-M-14}$ e $bla_{CTX-M-8}$. O Inc mais encontrado foi IncF ($n = 11$), classificado em seis replicons diferentes; seguido por IncII ($n = 5$), classificado no ST80 e ST131; e IncL/M ($n = 1$), em plasmídeos variando de 97-291 kb. O sequenciamento de genoma completo permitiu a detecção de outros genes de resistência a β -lactâmicos e a outras classes de antimicrobianos, bem como diversos genes de virulência. A presença de genes codificadores de ESBL e carbapenemase na microbiota comensal de indivíduos de uma comunidade remota no Brasil é um resultado inédito que demonstra que a disseminação de um problema endêmico em áreas urbanas para uma comunidade – em teoria – com baixa exposição a antibacterianos está acontecendo, sendo que as fontes e/ou veículos de aquisição são dignas de investigação, para um controle epidemiológico.

Palavras-chave: Resistência antimicrobiana. *Enterobacteriaceae*. ESBL. CTX-M. GES-5. MLST. Plasmídeos. Sequenciamento de genoma completo. Comunidade remota.

ABSTRACT

SILVA, Q. M. **Antimicrobial resistance in a remote community in the Amazon Forest.** 2017. 107 p. Ph.D. thesis (Microbiology) – Instituto de Ciências Biomédicas, Universidade de São Paulo, São Paulo, 2017.

Emergence and spread of multiresistant bacteria are closely related to antimicrobial misuse in human and veterinary medicine and livestock. However, some studies have reported the presence of these bacteria in remote communities with low or minimal exposure to antimicrobials. Thus, the aim of this study was to investigate the presence of plasmid-mediated β -lactamase in the commensal Gram-negative microbiota of humans and domestic animals of different indigenous ethnic groups in the Amazon Forest region, and to elucidate their genetic context. In March 2013, stool samples were collected from individuals attended in a health care center restricted to indigenous communities ($n = 36$) and from their local staff ($n = 9$). Additionally, in July 2013, rectal swab samples were collected from companion animals ($n = 20$) in the community. Bacterial species identification was performed by MALDI-TOF and antimicrobial susceptibility was assessed by the Kirby-Bauer technique. Antimicrobial resistance genes and *E. coli* phylo-groups were detected by PCR. Clonal relation among the isolates was investigated by ERIC-PCR and MLST. Plasmid mobility, size, and incompatibility groups (Inc) were evaluated by conjugation and transformation, S1-PFGE, and PBRT, respectively. Representative isolates of each clonal group were submitted to whole genome sequencing. Surprisingly, 30 isolates from humans and five isolates from animals have presented resistance to cephalosporins and fluoroquinolones. The presence of *bla*_{TEM-1} (78.6%) > *bla*_{CTX-M-15} (71.4%) > *bla*_{CTX-M-14} (21.4%) > *bla*_{CTX-M-8}, and *bla*_{GES-5} (1% each) genes was confirmed in 14 isolates (from 10 individuals), most of them identified as *E. coli* (70%). In addition, the presence of *bla*_{CTX-M-14} (60%) > *bla*_{TEM-1} (40%) > *bla*_{CTX-M-2}, and *bla*_{CTX-M-8} (20% each) genes was confirmed in five *E. coli* strains isolated from dogs. *E. coli* phylo-group D was predominantly found in both human ($n = 6$) and animal ($n = 4$) isolates. A clonal relationship was observed among five *E. coli* isolates from humans and three from animals, and all *K. pneumoniae* isolates were represented by a single clone. Plasmid mobility was observed in nine isolates harboring *bla*_{TEM-1}, *bla*_{CTX-M-15}, *bla*_{CTX-M-14}, and *bla*_{CTX-M-8} genes. IncF was the most prevalent Inc group ($n = 11$), classified in six different replicons; followed by IncI1 ($n = 5$), assigned to ST80 and ST131; and IncL/M ($n = 1$), in plasmids ranging from 97-291 kb. The whole genome sequencing allows the identification of other β -lactam resistance genes and genes conferring resistance to other antimicrobial classes, as well as several virulence genes. The presence of genes encoding ESBL and carbapenemase in the commensal microbiota of individuals from a remote community in Brazil is an unprecedented result. It demonstrates that the dissemination of an urban endemic problem to a community – in theory – with low antimicrobial exposure is occurring. Therefore, the sources and/or vehicles of acquisition are worthy of investigation in order to establish epidemiologic control measures.

Keywords: Antimicrobial resistance. *Enterobacteriaceae*. ESBL. CTX-M. GES-5. MLST. Plasmids. Whole genome sequencing. Remote community.

1 INTRODUÇÃO

Infecções causadas por bactérias resistentes a múltiplos antimicrobianos são um dos principais problemas de saúde pública no mundo. Essas bactérias estão associadas a altas taxas de morbidade e mortalidade e, também, a elevados custos hospitalares. O surgimento e a dispersão das mesmas estão estreitamente relacionados ao uso excessivo e inadequado de antimicrobianos nas práticas médica e veterinária e na produção animal (LYE et al., 2012; SCHWABER et al., 2006).

Contudo, os antimicrobianos não agem apenas sobre bactérias patogênicas, mas também sobre bactérias comensais, principalmente da microbiota intestinal. A pressão seletiva exercida pelo uso de antimicrobianos pode causar um significativo impacto na microbiota intestinal, promovendo o desenvolvimento de bactérias multi-resistentes, bem como diminuindo a resistência à colonização por outras bactérias e propiciando a transferência horizontal de genes de resistência (MACFARLANE, 2014).

O intestino de humanos e animais é o principal reservatório de bactérias multi-resistentes. Essas bactérias podem permanecer nele de forma assintomática, por longos períodos de tempo, e serem disseminadas no ambiente ou entre humanos e animais, por transmissão cruzada, sendo este um fator preponderante na ocorrência de infecções comunitárias (CARLET, 2012; WOERTHER et al., 2013a).

As bactérias gram-negativas, especialmente enterobactérias e não-fermentadoras, são as mais relacionadas à resistência antimicrobiana devido à diversidade de mecanismos de resistência que apresentam e à facilidade de disseminação de seus genes através de elementos genéticos móveis, como plasmídeos. A produção de β -lactamases é o principal mecanismo de resistência utilizado por essas bactérias (EL SALABI; WALSH; CHOUCANI, 2013).

Apesar de terem sua ocorrência na comunidade associada à pressão seletiva exercida pelo uso de antimicrobianos (DIAS et al., 2012; LEISTNER et al., 2013; RAJAPANDIYAN et al., 2014; WOERTHER et al., 2013a; WOLLHEIM et al., 2011), alguns estudos têm relatado a presença de bactérias produtoras de β -lactamases em comunidades remotas com baixa ou mínima exposição a antimicrobianos (BARTOLONI et al., 2004, 2009; PALLECCHI et al., 2007; WOERTHER et al., 2010, 2013b).

Os mecanismos pelos quais essas bactérias apresentam esse fenótipo de resistência, independentemente da pressão seletiva exercida pelo uso de antimicrobianos, ainda não estão bem elucidados. Portanto, a pesquisa de bactérias multi-resistentes e a compreensão dos mecanismos pelos quais elas se estabelecem em comunidades remotas, são fundamentais para

o estabelecimento de medidas de controle da disseminação da resistência nessas comunidades e, também, para traçar estratégias de prevenção do surgimento da resistência em outras comunidades em condições semelhantes.

6 CONCLUSÕES

- Foi detectada a presença de enterobactérias produtoras de β -lactamases na microbiota comensal de humanos e animais domésticos de uma comunidade remota no interior do estado do Amazonas;
- A espécie bacteriana prevalente entre os isolados foi *E. coli*, seguida por *K. pneumoniae*;
- Quatorze isolados de origem humana e cinco isolados de origem animal apresentaram perfil fenotípico para produção de ESBL e resistência a múltiplas classes de antimicrobianos;
- Os genes codificadores de ESBL mais encontrados foram *bla*_{CTX-M-15} e *bla*_{CTX-M-14};
- Um isolado de origem humana apresentou resistência a cefalosporinas e imipenem e foi detectada, pela primeira vez no mundo, a presença do gene *bla*_{GES-5} em *M. morganii*;
- Foi observada uma diversidade clonal entre os isolados de *E. coli*, com detecção de STs mundialmente disseminados e também de um novo ST de *E. coli* (ST6993);
- Os isolados de *K. pneumoniae* foram representados por um único clone (ST198);
- Alguns isolados de *E. coli* de humanos e animais foram clonalmente relacionados, sugerindo a disseminação dessas bactérias entre esses hospedeiros;
- Apenas nove plasmídeos carregando os genes *bla*_{CTX-M-14} ($n = 4$), *bla*_{CTX-M-15} ($n = 3$) e *bla*_{CTX-M-8} ($n = 2$) foram mobilizados, pela técnica de conjugação;
- O gene *bla*_{GES-5} e dois genes *bla*_{CTX-M-14} foram encontrados no cromossomo;
- Os grupos de incompatibilidade plasmidial encontrados (IncF, IncII e IncL/M) estão entre os mais disseminados no mundo;
- IncF e IncII foram associados aos genes *bla*_{CTX-M-15} e *bla*_{CTX-M-14}, respectivamente;
- Os plasmídeos da família IncF foram caracterizados por diferentes replicons, enquanto todos os plasmídeos do IncII foram pertencentes ao ST80;
- Os resultados deste trabalho demonstram a disseminação de um problema endêmico de áreas urbanas para uma comunidade remota, em teoria, com baixa exposição a antibióticos.

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