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Epidemiology of Invasive Group B Streptococcal Disease in Alberta, Canada, from 2003 to 2013

Alhhazmi A, Hurteau D, Tyrrell GJ.

1. Division of Diagnostic and Applied Microbiology, Department of Laboratory Medicine and Pathology, University of Alberta, Edmonton, Alberta, Canada.

2. Provincial Laboratory for Public Health (Microbiology), Edmonton, Alberta, Canada.

3. Division of Diagnostic and Applied Microbiology, Department of Laboratory Medicine and Pathology, University of Alberta, Edmonton, Alberta, Canada Provincial Laboratory for Public Health (Microbiology), Edmonton, Alberta, Canada.

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The present is a surveillance study on invasive infections due to GBS in Alberta, Canada. Between 2003 and 2013 they received 1683 invasive isolates recovered from neonatal infections (early onset disease, EOD and late onset disease, LOD) and from adult patients. The disease incidence rate increased from 3.92 to 5.99 cases/100,000 population due to multifactorial events that are hypothesized by the authors. Capsular polysaccharide (CPS) III (20.3%), CPS V (19.1%) and CPS Ia (18.9%) were the most predominant types, followed by Ib (12.7%), II (11.1%) and IV (6.3%) and 9.4% of the isolates were nontypeable. It is noticeable the increased in serotype IV from 2 isolates to 24 in 2013 of which the majority were hvgA positive (86.6%), ST459 and CC1. HvgA is an adhesin involved in colonization associated to GBSCC17, CC1 and CC23 clones but in this work was associated to CC1. In 2013 the prevalent sequence type was ST459. Even though the application of the intrapartum prophylaxis in Canada, in the studied period EOD increase from 0.15 to 0.34 cases/100,000 live births and LOD increases from 0.15 to 0.39 cases/100,000 live births. So, the authors considered that the continuous surveillance is necessary to monitor the changes. In the period studied erythromycin and clindamycin resistance increased from 23.6% to 43.9% and from 12.2 to 32.5% respectively. In summary, Alberta has experienced an increase in GBS disease, both in neonatal and adult disease, an increase in CPS IV cases, and also an increase in the resistance to erythromycin and clindamycin.

En Alberta, Canadá, los autores estudiaron aislamientos de *S. agalactiae* (EGB) obtenidos en el período de tiempo comprendido entre 2003-2013. Ellos fueron recuperados de infecciones invasivas neonatales tempranas (EOD) y tardías (LOD) y también de adultos. La incidencia de enfermedad aumentó del 3,92 al 5,99 casos/100,000 habitantes, debido a causas multifactoriales comentadas por los autores en el trabajo. Los serotipos capsulares prevalentes fueron el III (20,3%), V (19,1%) y Ia (18,9%) seguidos por el Ib (12,7%), II (11,1%) y IV (6,3%). El 9,4% no pudo ser tipificado. Es importante destacar el aumento del número de aislamientos del serotipo IV de los cuales la mayoría presentaron el gen hvgA (86,6%), el ST459 (que además

fue el ST prevalente de todos los aislamientos del estudio) y el CC1. La proteina HvgA es una adhesina involucrada en la colonización y se reportó su asociación con GBS-CC17, CC1 y CC23. En este trabajo solo se la asoció al CC1. A pesar del uso de la profilaxis intraparto en Canadá, en el período de estudio la EOD aumentó del 0,15 al 0,34 casos/100.000 nacimientos vivos y la LOD presentó un aumento del 0,15 al 0,39 casos/100.000 nacidos vivos. Es por ello que los autores consideran necesario el monitoreo continuo. En el período estudiado la resistencia a eritromicina y a clindamicina aumentó del 23,6% al 43,9% y del 12,2 al 32,5% respectivamente. En resumen, en Alberta se registró un aumento de la enfermedad por SGB, un aumento del serotipo IV y un aumento de la resistencia a eritromicina y clindamicina.

Differential antimicrobial susceptibilities of *Granulicatella adiacens* and *Abiotrophia defectiva*.

Mushtaq A[1], Greenwood-Quaintance KE[1], Cole NC[1], Kohner PC[1], Ihde SM[1], Strand GJ[1], Harper LW[1], Virk A[2], Patel R[3].

1. Division of Clinical Microbiology, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota, USA.

2. Division of Infectious Diseases, Department of Medicine, Mayo Clinic, Rochester, Minnesota, USA.

3. Division of Clinical Microbiology, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota, USA Division of Infectious Diseases, Department of Medicine, Mayo Clinic, Rochester, Minnesota, USA patel.robin@mayo.edu.

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Abiotrophia and *Granulicatella* species (referred to as nutritionally variant streptococci) can cause various infections, mainly endocarditis. Current guidelines for the treatment of *Granulicatella* or *Abiotrophia* endocarditis are listed in the table.

Table. Current guidelines for the treatment of *Granulicatella* or *Abiotrophia* endocarditis.

Society	Beta-lactams	Length	Vancomycin (length)	Aminoglycosides (length)
British Society of Antimicrobial Chemotherapy	Benzylpenicillin	4 – 6 weeks	-	4 – 6 weeks
European Society of Cardiology	Penicillin G Ceftriaxone	6 weeks	6 weeks	At least the 2 first weeks
American Heart Association	Ampicillin Penicillin Ceftriaxone (if susceptible)	Determined by the infectious diseases department	Patients intolerant of beta-lactams	Determined by the infectious diseases department

MICs of 25 *Abiotrophia defectiva* and 109 *Granulicatella adiacens* isolates were determined by broth microdilution (Sensititre® with Mueller Hinton broth + 2,5% lysed horse blood + 0.001% pyridoxal). Using CLSI breakpoints, the susceptibilities of *A. defectiva* and *G. adiacens* isolates were, respectively, 24% and 34% to penicillin, 92% and 22% to ceftriaxone, 48% and 3% to cefepime, 72% and 87% to meropenem, 92% and 10% to cefotaxime, 100% and 97% to levofloxacin, 92% and 80% to clindamycin, and 24% and 50% to erythromycin. All isolates were susceptible to vancomycin. Of note, in the penicillin-susceptible subgroup, all *A. defectiva* isolates were susceptible to ceftriaxone; however, 62% of *G. adiacens* isolates were ceftriaxone nonsusceptible.

Comments: authors highlight the good reproducibility of the in vitro studies to recommend routine performance of dlution tests for these organisms. I agree with this experience, but taking into account of disociation of in vivo and in vitro observed by Bouvet *et al*. during the 80's and the frequent failures of treatment of endocarditis due to *Granulicatella* and *Abiotrophia* in spite of low MICs of beta-lactams, I think that the problema is not the quality of susceptibility tests, but the special behavior of these organisms in vivo. However, according of this study, the accurate identification at species level would let us discard the option of ceftriaxone if any *Granulicatella* species is detected, and, then, by means of in vitro susceptibility tests, select the best antibiotic combination.

Las especies de *Abiotrophia* y *Granulicatella* species (conocidas como variantes nutricionales de los estreptococos) pueden causar una variedad de infecciones, principalmente endocarditis. Las guías disponibles para el tratamiento de endocarditis por *Granulicatella* o *Abiotrophia* pueden verse en la tabla.

Tabla. Guías para el tratamiento de endocarditis por *Granulicatella* o *Abiotrophia*

Sociedad	Beta-lactámicos	Duración	Vancomicina (duración)	Aminoglucósidos (duración)
British Society of Antimicrobial Chemotherapy	Bencilpenicilina	4 – 6 semanas	-	4 – 6 semanas
European Society of Cardiology	Penicilina G Ceftriaxona	6 semanas	6 semanas	Al menos las dos primeras semanas
American Heart Association	Ampicilina Penicilina Ceftriaxona (si fuera sensible)	Determinada por el departamento de Infectología	Pacientes intolerantes a los beta-lactámicos	Determinada por el departamento de Infectología

Se determinó la CIM de 25 aislamientos de *Abiotrophia defectiva* y 109 de *Granulicatella adiacens* por microdilución (Sensititre® con caldo Mueller Hinton + 2,5% de langre lisada de caballo + 0,001% de piridoxal). Usando los puntos de corte del CLSI la sensibilidad de *A.*

defectiva y *G. adiacens* fueron, respectivamente, 24% y 34% a penicilina, 92% y 22% to ceftriaxona, 48% y 3% a cefepima, 72% y 87% a meropenem, 92% y 10% a cefotaxima, 100% y 97% a levofloxacina, 92% y 80% a clindamicina y 24% y 50% a eritromicina. Todos los aislamientos fueron sensibles a vancomicina. Es notable que en el subgrupo de bacterias sensibles a penicilina, todos los aislamientos de *A. defectiva* hayan sido sensibles a ceftriaxona y, en cambio, 62% de los correspondientes a *G. adiacens* hayan sido "no sensibles" a ese antibiótico.

Comentario: Los autores destacan la buena reproducibilidad de los estudios *in vitro* y recomiendan la realización rutinaria de pruebas de dilución para estos microorganismos. Estoy de acuerdo con esa experiencia, pero si se toma en cuenta la disciación *in vivo - in vitro* observada por Bouvet et al. en la década de los 80 y las frecuentes fallas de tratamiento de endocarditis por *Granulicatella* o *Abiotrophia* a pesar de los bajos valores de CIM de los beta-lactámicos, pienso que el problema no es la falta de calidad de las pruebas de sensibilidad, sino la conducta especial de estos microorganismos *in vivo*. Sin embargo, de acuerdo con este trabajo, la identificación correcta a nivel de especie nos permitiría descartar inicialmente la opción del uso de ceftriaxona cuado se aísle alguna especie de *Granulicatella* y luego seleccionar la combinación más apropiada a tavés de ensayos de sensibilidad *in vitro.*

Influence of MIC in Clinical Outcomes of *Enterococcus faecium* Bacteremia Treated with Daptomycin: Is It Time to Change the Breakpoint?

Bhavarth S. Shukla[1,2], Samuel Shelburne[2,3], Katherine Reyes[4], Mini Kamboj[5], Jessica D. Lewis[6], Sandra L. Rincon[1,7], Jinnethe Reyes[7], Lina P. Carvajal[7], Diana Panesso[1,7], Costi D. Sifri[6], Marcus J. Zervos[4,8], Eric G. Pamer[5], Truc T. Tran[1], Javier Adachi[2], Jose M. Munita[1,9], Rodrigo Hasbun[1], Cesar A. Arias[1,7,*]

1. University of Texas Medical School at Houston, Houston, TX, USA.

2. Department of Infectious Diseases, M.D. Anderson Cancer Center, Houston, Texas, USA.

3. Genomic Medicine, M.D. Anderson Cancer Center, Houston, Texas, USA.

4. Department of Internal Medicine, Division of Infectious Diseases, Henry Ford Hospital, Detroit, MI, USA.

5. Memorial Sloan Kettering Cancer Center, New York, NY, USA.

6. Division of Infectious Diseases and International Health, Department of Medicine, University of Virginia Health System, Charlottesville, VA, USA.

7. Molecular Genetics and Antimicrobial Resistance Unit, Universidad El Bosque, Bogota, Colombia.

8. Wayne State University School of Medicine, Detroit, MI, USA.

9. Clinica Alemana, Universidad del Desarrollo, Santiago, Chile.

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Daptomycin has become a first-line antibiotic for multidrug-resistant *E. faecium* bloodstream infections. The present is a multicenter (4 sites) retrospective cohort study (2010 - 2015) that included adult patients with *E. faecium* bloodstream infection for whom initial isolates, follow-up blood culture data, and daptomycin administration data were available. They performed standardized daptomycin MIC testing for all isolates. The primary outcome was microbiologic failure, defined as clearance of bacteremia occurring ≥4 days after the index blood culture. The secondary outcome was all-cause in-hospital mortality.

A total of 62 patients were included. Daptomycin MICs by Etest method were equally distributed with 31 patients exhibiting a daptomycin MIC of ≤ 2 µg/mL and 31 with MICs of 3-4 µg/mL. All daptomycin MICs by broth microdilution method were ≤ 2 µg/mL.

Fifty five percent of the patients infected with isolates exhibiting daptomycin MICs of 3-4 µg/mL had microbiologic failure and 40% died during hospitalization. On a multivariate logistic regression model, daptomycin MICs of 3-4 µg/mL (OR 4.7 [1.37-16.12], p=0.014) and immunosuppression (OR 5.32 [1.20-23.54], p=0.028) were significantly associated with microbiologic failure, while initial daptomycin dose of ≥8 mg/kg was not significantly associated with evaluated outcomes.

The authors suggest that the current CLSI breakpoint for daptomycin in enterococci (4 µg/mL) should be reevaluated. On the other hand, they indicate that broth microdilution is not robust enough to identify subpopulations of resistant bacteria (similar to the phenomenon of vancomycin non-susceptibility in *S. aureus*).

They conclude that daptomycin MICs of 3-4 µg/mL in the initial *E. faecium* blood isolate predicted microbiological failure of daptomycin therapy.

La daptomicina se ha convertido en un antibiótico de primera línea para bacteriemias por *E. faecium* multirresistentes. El presente es un estudio multicéntrico (4 centros) retrospectivo (2010-2015), que incluyó pacientes adultos con bacteriemia por *E. faecium* de los que se disponía de los aislamientos primarios, hemocultivos de seguimiento, y datos de administración de daptomicina. Se determinó la CIM de daptomicina a todos los aislamientos. Evaluaron en primer lugar el fracaso microbiológico, definido como la negativización de los hemocultivos ocurrida ≥ 4 días después del hemocultivo inicial positivo. En segundo lugar evaluaron las causas de mortalidad hospitalaria.

Se incluyeron 62 pacientes, que de acuerdo a la CIM de daptomicina por Etest se distribuyeron en 31 pacientes con CIM ≤ 2 mg/ml y 31 pacientes con CIM de 3-4 mg/ml. Por el método de microdilución en caldo todos los aislamientos presentaron CIM de daptomicina ≤ 2 mg/ml. Entre los pacientes infectados con cepas con CIM de daptomicina de 3-4 mg/ml, el 55% presentó falla microbiológica y el 40% murió durante la hospitalización. En un modelo de regresión multivariado, las CIM de daptomicina de 3-4 mg/ml (OR 4,7 [1,37-16,12], p = 0,014) y

la inmunosupresión (OR 5,32 [1,20 a 23,54], p = 0,028) se asociaron significativamente con la falla microbiológica, mientras que la dosis inicial de daptomicina ≥8 mg / kg no se asoció significativamente con los resultados evaluados.
Los autores sugieren que el actual punto de corte del CLSI para daptomicina en los enterococos (4 mg/ml) debe ser reevaluado. Por otro lado, indican que el método de microdilución en caldo no es lo suficientemente robusto para identificar subpoblaciones de bacterias resistentes (similar al fenómeno de *S. aureus* no sensibles a vancomicina).
Llegan a la conclusión de que el aislamiento de *E. faecium* con CIM a daptomicina de 3-4 mg/ml en el hemocultivo inicial predijo el fracaso microbiológico del tratamiento con daptomicina.

We are reproducing here the letter sent by organizers of the next Lancefield Symposium:

SAVE THE DATE

"We are proud to announce that the 20th Lancefield International Symposium on Streptococci and Streptococcal Diseases will be held in Fiji from the 16th to 20th October 2017.

The 20th LISSSD will continue the tradition of linking laboratory excellence with high quality clinical and epidemiologic studies of streptococcal infections, but will bring a fresh and forward-looking approach with a focus on cutting-edge science, and on streptococcal disease in endemic regions. The 20th LISSSD will be held in the stunning location of the Sofitel Hotel on Denarau Island on the west coast of Fiji, providing a beautiful and relaxing setting to discuss research ideas and collaboration, and providing easy access to some of the most picturesque islands in the world.

Please visit the conference website to register your interest and be kept up-to-date with conference arrangements as they unfold.

We very much look forward to your participation in the 20th LISSSD in Fiji.

20th LISSSD Co-Chairs

Associate Professor Joseph Kado & Associate Professor Andrew Steer

20th LISSSD Vice Co-Chairs

Professor Mark Walker and Professor Pierre Smeesters

On behalf of the Organising and Scientific Committees"