

INVASIVE GROUP A STREPTOCOCCAL DISEASE: RACE, HYPOTENSION, AND IMMUNOGENETICS

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Objective: To determine if there was an association between race and the incidence of hypotension among patients hospitalized for invasive group A streptococcal disease (IGASD).

Design: Data were obtained from a retrospective cohort study of IGASD patients. The subjects were hospitalized throughout Florida for IGASD between 1996 and 2000 (N=151). The exposure variable for the current study was race (African Americans, Caucasians). The binary outcome was the presence of hypotension within 48 hours of hospital admission. A sensitivity analysis was performed to determine if a particular human leukocyte antigen (HLA) class II haplotype (DRB1*1501/DQB1*0602) confounded the association between race and the risk of hypotension. IGASD patients possessing this haplotype are less likely to experience hypotension with multiple organ failure.

Results: We found that Caucasians had three times the odds of developing hypotension than African Americans (adjusted odds ratio=3.02, 95% confidence interval: 1.10–8.29, P=.03). The sensitivity analysis revealed that the HLA class II haplotype DRB1*1501/DQB1*0602 was most likely not a confounder.

Conclusions: Caucasians were significantly more likely than African Americans to develop the adverse outcome of hypotension within 48 hours of being hospitalized for IGASD. This excess risk is most likely not due to a particular host genetic factor, the HLA class II haplotype DRB1*1501/DQB1*0602. (*Ethn Dis.* 2005; 15 [suppl 5]:S5-63–S5-66)

Key Words: African Americans, European Continental Ancestry Group, HLA-DQ Antigens/Genetics, HLA-DR Antigens/Genetics, Hypotension, *Streptococcus Pyogenes*

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INTRODUCTION

Invasive group A streptococcal disease (IGASD) is a disease of major public health importance in the United States. Nationwide, it is estimated that more than 8,000 cases of IGASD occur annually.¹ This incidence is twice that of the reported incidence of *E. coli* O157:H7 infections and four times the annual reported incidence of meningococcal disease.¹ The popular press has dubbed the etiologic organism, *Streptococcus pyogenes*, the “flesh-eating” bacterium. IGASD can lead to multiple severe outcomes such as hypotension, amputation, and death,² with a case-fatality rate as high as 45%.³ In the United States, the crude incidence of IGASD is higher among African Americans than Caucasians.⁴

It has become apparent that host genetic factors may alter the risk of developing certain infectious diseases or modify the risk of a severe outcome among patients who have already developed the disease.⁵ Kotb et al recently studied the outcomes of IGASD patients in Ontario, Canada.⁵ These investigators found that IGASD patients who possessed a particular human leukocyte antigen (HLA) class II haplotype (DRB1*1501/DQB1*0602) mounted a significantly reduced cytokine response and were less likely to have severe systemic disease than IGASD patients with other HLA class II haplotypes. Severe systemic disease was defined as the presence of hypotension and multiple organ failure.

The objective of this retrospective cohort study was to determine if there was an association between race and the incidence of hypotension among patients hospitalized for IGASD through-

out Florida. We also performed a sensitivity analysis to determine if the DRB1*1501/DQB1*0602 haplotype confounded the association between race and the risk of hypotension.

METHODS

Setting

This study was a secondary analysis of a retrospective cohort study that was conducted in Florida. The methods of the original study are described in detail elsewhere.⁶

The original study population was comprised of 195 patients who were hospitalized for IGASD and reported to the Florida Department of Health (Tallahassee, Florida) between August 1996 and August 2000. IGASD was defined as isolation of group A *Streptococcus* from a normally-sterile site or isolation from a nonsterile site in a patient with necrotizing fasciitis. Surveillance data were obtained from the Florida Department of Health and included demographic and clinical data for these IGASD patients. The original study protocol was approved by the Florida Department of Health and the University of South Florida Medical institutional review board. The current study was approved by the Committee for the Protection of Human Subjects at the University of Texas Health Science Center at Houston.

Statistical Analysis

The SAS System for Windows 8.02 (SAS Institute, Inc, Cary, North Carolina) was used to perform logistic regression. The exposure of interest was race (Caucasian or African-American). The binary outcome was the

presence of hypotension within 48 hours of admission to the hospital. The development of hypotension was noted on the Florida Department of Health surveillance case report form for IGASD.

The change-in-estimate method⁷ was used to determine if the following variables were confounders of the association under study: age (a continuous variable), sex, presence of coronary heart disease (yes/no), presence of necrotizing fasciitis (yes/no), use of beta-lactam antibiotics during the hospital stay (yes/no), and use of the antibiotic clindamycin during the hospital stay (yes/no). The change-in-estimate method, unlike forward selection or backward elimination, does not rely on *P* values to choose covariates for inclusion in the final model. This technique, rather, relies on a change in the race odds ratio when one or more potential confounders are added to the model.⁷ We used a 15% change to build our model.

Multiple logistic regression analyses can only be performed if every patient record has complete data for all of the independent variables and the dependent variable. After deleting records that had missing values for the variables under study, 168 records were identified. We excluded one Asian/Pacific Islander, one African-American Hispanic, 10 Caucasian Hispanics, and five patients with an unknown value for Hispanic ethnicity. A total of 151 patient records were available for logistic regression.

Finally, a sensitivity analysis was performed to determine if the association between race and hypotension was confounded by the DRB1*1501/DQB1*0602 haplotype.⁸ Our original study was retrospective and therefore patient specimens were not available for HLA class II genotyping. A sensitivity analysis allows an investigator to adjust for an unmeasured potential confounder assuming external data are available.

Table 1. Clinical and demographic characteristics of 151 patients hospitalized for invasive group A streptococcal disease

Characteristic	Caucasian* (n=126)	African American† (n=25)
	N (%)	N (%)
Male	62 (49)	11 (44)
Coronary heart disease	32 (25)	5 (20)
Necrotizing fasciitis	26 (21)	3 (12)
Beta-lactams	102 (81)	22 (88)
Clindamycin	38 (30)	4 (16)

* Median age (Minimum – Maximum): 54 years (0 years – 103 years).
 † Median age (Minimum – Maximum): 60 years (3 years – 83 years).

Data for our sensitivity analysis were obtained from a study by Kotb and colleagues.⁵ Kotb et al studied the immunogenetics of 152 IGASD patients from Canada. These patients were classified into one of two outcomes: cases with severe systemic disease, or cases without severe systemic disease. Severe systemic disease was defined as the presence of hypotension and multiple organ failure. The frequency of the DRB1*1501/DQB1*0602 haplotype in cases with severe systemic disease was 11% while the frequency of this protective haplotype among cases without severe systemic disease was 34% (crude odds ratio=0.25, 95% confidence interval: 0.09–0.68). After adjusting for potential confounders (age, the serotype of the infecting strain, and the presence of necrotizing fasciitis) this odds ratio did not change appreciably (adjusted odds ratio=0.24). The adjusted odds ratio indicates that IGASD patients who possessed this protective haplotype had a 76% reduction in the odds of severe systemic disease compared to IGASD patients who did not possess the protective haplotype. We used this odds ratio (0.24) along with a less extreme odds ratio (0.50) and a more extreme odds ratio (0.10) in our calculations.

Our sensitivity analysis also required estimates of the frequency of the protective haplotype by race. In the Canadian study described above, the overall prevalence of the protective haplotype (DRB1*1501/DQB1*0602) was 28%

(42/152). These 152 patients were Caucasian (M Kotb, personal communication, July 2004). From this finding, we initially assumed that 28% of our Florida Caucasian patients had the protective haplotype. We then varied this figure to minimize the probability that we had misspecified the prevalence among Florida Caucasians. To our knowledge, there are no published reports of the frequency of this protective haplotype among African Americans hospitalized for IGASD. For our calculations, we assumed that the prevalence of this haplotype was higher among our African-American patients than our Caucasian patients. This assumption was based on observations from our previous studies that indicated that the African-American patients had a lower frequency of admission into an intensive care unit, and African Americans appeared to have a lower hospital mortality rate than Caucasians.^{6,9} A plausible range for the prevalence of this protective haplotype among African Americans was derived after examining an HLA class II haplotype database.¹⁰

RESULTS

Table 1 shows the distribution of potential confounders by exposure status. The African Americans were older than the Caucasians but had a lower prevalence of coronary heart disease.

Table 2. Odds ratios for hypotension (Caucasians compared to African Americans) among 151 patients hospitalized for invasive group A streptococcal disease

Variable(s) in the Model	Odds Ratio	95% Confidence Interval
Race	3.37	1.26–9.01
Race, age, sex, coronary heart disease, necrotizing fasciitis, beta-lactams, clindamycin	3.02	1.10–8.29

The incidence of hypotension among Caucasians and African Americans was 52% (65/126) and 24% (6/25), respectively. The six variables shown in Table 1 did not confound the association between race and hypotension either individually or jointly. Adjusting for these six covariates simultaneously revealed that the crude and adjusted race odds ratios differed by less than 15% (Table 2). Both the crude and adjusted odds ratios indicated that Caucasians had approximately three times the odds of developing hypotension than African Americans.

The sensitivity of the externally adjusted race-hypotension odds ratio is displayed in Table 3. The odds ratios of 0.10, 0.24, and 0.50 summarize the association between the potential confounder (the protective haplotype described above) and the outcome of hypotension. The 18 odds ratios that are adjusted for the protective haplotype are shown in the body of the table. Adjusting for the protective haplotype attenuated the crude odds ratio of 3.37; however, this dilution of the odds ratio

was minimal (<15%) for 17 of the 18 adjusted odds ratios.

DISCUSSION

This analysis revealed that, among a cohort of patients hospitalized in Florida for IGASD, Caucasians were significantly more likely than African Americans to develop the adverse outcome of hypotension within 48 hours of admission. This result is consistent with a finding from our earlier study.⁶ Our original study found that African Americans appeared to have a lower hospital mortality rate than the Caucasians (crude odds ratio 0.31, 95% CI 0.09–1.08).⁶

A potential confounder of the association under study was the HLA class II haplotype DRB1*1501/DQB1*0602.⁵ Our database did not contain information on this host genetic factor and therefore data from a Canadian study were used to perform a sensitivity analysis.⁵ Our analysis indicates that, although there was a

distinct difference in outcomes between African Americans and Caucasians, this difference was most likely not the result of the host genetic factor HLA class II haplotype DRB1*1501/DQB1*0602.

A limitation of the sensitivity analysis was the discrepancy between our outcome variable (hypotension) and the outcome in the Canadian study (hypotension plus multiple organ failure). To minimize the effect of this limitation, we used an odds ratio that was more conservative than the one reported by the Canadian investigators (0.50 vs 0.24) for the relationship between this haplotype and the development of hypotension and, an odds ratio that was more extreme (0.10 vs 0.24). We could not study the outcome of hypotension plus multiple organ failure due to the limited amount of laboratory data, such as liver function tests and creatinine levels, in our database.

Another potential limitation was our assumption that the prevalence of this protective haplotype among Florida Caucasians was similar to that of Canadian Caucasians (28%). However, we feel that any bias is minimized by our use of a range of plausible estimates (25%–34%). Furthermore, these variations did not change our conclusion regarding the confounding potential of this haplotype.

It is possible that the association between race and hypotension in our study was confounded by hypertension. African Americans tend to have a higher prevalence of hypertension than Caucasian Americans. Chronic arterial hypertension in rats protects against mortality from sepsis.¹¹ Several of our cases had admitting diagnoses of sepsis, and the majority of these 151 patients (127 or 84%) had group A streptococcal bacteremia. Even though data are lacking in humans, hypertension may protect against hypotension and shock in the setting of sepsis which may lead to a reduced risk of mortality.¹¹

Table 3. Results of the sensitivity analysis: odds ratios for hypotension (Caucasians compared to African Americans) adjusted for a protective HLA class II haplotype using external data

P _{Z1}	P _{Z0}	Three Odds Ratio for Hypotension (Has Protective Haplotype vs Lacks Protective Haplotype)		
		0.10	0.24	0.50
0.25	0.35	AOR=2.98	AOR=3.06	AOR=3.18
0.25	0.40	2.79	2.90	3.09
0.28	0.35	3.09	3.15	3.24
0.28	0.40	2.89	2.98	3.14
0.34	0.35	3.33	3.34	3.35
0.34	0.40	3.11	3.17	3.25

HLA=human leukocyte antigen; P_{Z1}=prevalence of protective haplotype among Caucasians; P_{Z0}=prevalence of protective haplotype among African Americans; AOR=adjusted odds ratio.

CONCLUSION

Caucasians were significantly more likely than African Americans to develop the adverse outcome of hypotension within 48 hours of being hospitalized for IGASD. This excess risk is most likely not due to a particular host genetic factor, the HLA class II haplotype DRB1*1501/DQB1*0602.

REFERENCES

1. Centers for Disease Control and Prevention. Summary of notifiable diseases—United States, 2000. *Morb Mortal Wkly Rep.* 2002;49.
2. Mulla ZD. Treatment options in the management of necrotising fasciitis caused by group A *Streptococcus*. *Expert Opin Pharmacother.* 2004;5(8):1695–1700.
3. O'Brien KL, Beall B, Barrett NL, et al. Epidemiology of invasive group A *Streptococcus* disease in the United States, 1995–1999. *Clin Infect Dis.* 2002;35(3):268–276.
4. Group A *Streptococcus* Surveillance Report, Preliminary 2003. Centers for Disease Control and Prevention. Available at: www.cdc.gov. Accessed on: 2/24/05.
5. Kotb M, Norrby-Teglund A, McGeer A, et al. An immunogenetic and molecular basis for differences in outcomes of invasive group A streptococcal infections. *Nat Med.* 2002;8(12):1398–1404.
6. Mulla ZD, Leaverton PE, Wiersma ST. Invasive group A streptococcal infections in Florida. *South Med J.* 2003;96(10):968–973.
7. Greenland S. Modeling and variable selection in epidemiologic analysis. *Am J Public Health.* 1989;79(3):340–349.
8. Greenland S. Basic methods for sensitivity analysis and external adjustment. In: Rothman KJ, Greenland S, eds. *Modern Epidemiology*. 2nd ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 1998:343–357.
9. Mulla ZD. Invasive group A streptococcal disease and intensive care unit admissions. *Intensive Care Med.* 2002;28(12):1822–1824, [Erratum: *Intensive Care Med.* 2003; 29:665].
10. Allele Frequencies in Worldwide Populations. Available at: www.allelefrequencies.net. Accessed on: 7/20/04.
11. Nunes JP. Arterial hypertension and sepsis. *Rev Port Cardiol.* 2003;22(11):1375–1379.