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Clinical and epidemiological features of group A streptococcal bacteraemia in a region with hyperendemic superficial streptococcal infection

J. R. CARAPETIS, A. M. WALKER, M. HIBBLE, K. S. SRIPRAKASH* AND B. J. CURRIE

Menzies School of Health Research and Royal Darwin Hospital, Darwin, Australia

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SUMMARY

Reports of increasing incidence and severity of invasive group A streptococcal (GAS) infections come mainly from affluent populations where exposure to GAS is relatively infrequent. We conducted a 6-year retrospective review of GAS bacteraemia in the Northern Territory of Australia, comparing the Aboriginal population (24% of the study population), who have high rates of other streptococcal infections and sequelae, to the non-Aboriginal population. Of 72 episodes, 44 (61%) were in Aboriginal patients. All 12 cases in children were Aboriginal. Risk factors were implicated in 82% of episodes (91% in adults) and there was no significant difference in the proportion of Aboriginal compared to non-Aboriginal patients with at least one risk factor. Genetic typing of isolates revealed no dominant strains and no evidence of a clone which has been a common cause of these infections elsewhere.

INTRODUCTION

Over the past decade there have been numerous reports indicating a resurgence in group A streptococcal (GAS) invasive disease of increasing severity, often associated with M serotypes 1 and 3 and the production of streptococcal pyrogenic exotoxins [1–4]. However, most of these studies have taken place in affluent populations in industrialized countries. Other than pharyngitis during childhood, most GAS infections are now uncommon in these populations. By contrast, the level of exposure to GAS and the incidence of streptococcal pyoderma and post-streptococcal diseases is much greater in developing countries. It is not clear whether the increasing incidence and severity of invasive GAS infections seen in affluent populations in recent years has also occurred in these less affluent populations, or whether different patterns of exposure to GAS may alter the incidence or severity of invasive infections. We conducted a review of GAS bacteraemia in the Northern Territory, Australia, in a population with high rates of streptococcal pyoderma, rheumatic fever and acute post-streptococcal glomerulonephritis.

* Author for correspondence: Menzies School of Health Research, PO Box 41096, Casuarina NT 0811, Australia.

METHODS

Setting

The 'Top End' consists of approximately the northern third of the Northern Territory, Australia and has a population of 134709 people, 32472 (24%) of whom are Aboriginal (Australian Bureau of Statistics). Aboriginal people live mainly in remote, isolated communities with high levels of poverty and poor access to medical care [5], whereas non-Aboriginal people live mainly in affluent urban centres. Aboriginal people experience very high rates of acute rheumatic fever, rheumatic heart disease, acute post-streptococcal glomerulonephritis, and streptococcal pyoderma which is often secondary to scabies infestation [6–8]. Royal Darwin Hospital is the major

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teaching hospital in the Top End, providing primary, secondary and tertiary services. Royal Darwin Hospital has 300 beds, with an average of 18000–20000 discharges per year, 7000–8000 Aboriginal and 12000–13000 non-Aboriginal.

Case review

Cases of GAS bacteraemia for the 6-year period from January 1991 to December 1996 were ascertained from blood culture records of the bacteriology laboratory at Royal Darwin Hospital. Medical charts were reviewed for clinical and demographic data. For two of the 70 cases identified, medical charts were unavailable but data on age at diagnosis, gender and ethnicity were available, and one of these patients also was known to have died with septic shock as a complication of bacteraemia. These two cases together with a further two cases ascertained from the records of the Darwin Private Hospital were included in calculations of incidence rates and years of diagnosis but excluded from the analysis of clinical features, although the patient who died was included in the analysis of outcomes. The Darwin Private Hospital serves mainly non-Aboriginal clients and these patients were assumed to be non-Aboriginal in the incidence rate calculation.

There were six patients with repeated GAS bacteraemia and we analysed the clinical data for 68 episodes of bacteraemia in 59 individual patients. Data on sex and age at first diagnosis were available for 61 patients. Streptococcal toxic shock syndrome was defined using the criteria of the Working Group on Severe Streptococcal Infections [9].

Underlying risk factors were defined as any conditions which may have predisposed the patient to infection. 'Skin sores' was used as a generic term to refer to any of impetigo, infected skin ulcers, pressure sores, wound infection or boils. A patient was considered to have a delay in response to treatment if fever persisted for more than 48 h after commencement of parenteral antimicrobial chemotherapy to which the organism was sensitive. Persistent infection was defined as a positive blood culture or positive culture from another normally sterile site more than 24 h after commencement of appropriate antimicrobial chemotherapy. Complications were defined as death, streptococcal toxic shock syndrome, persistent infection, delayed response to treatment, or other variation from the expected rate of recovery once appropriate treatment was started. Patients were classified as children if they were aged 15 years or under, and adults if they were aged 16 years or over.

Incidence rates

Crude incidence rates for hospitalized cases of GAS bacteraemia in the Top End were calculated using as denominators the mean population for the entire period, calculated from adjusted Census data; these data compensate for the under counting of rural Aboriginal people in the Census, as described elsewhere [6]. The mean estimated population for these 6 years was 129577 people (98737 non-Aboriginal people and 30840 Aboriginal people). Age-standardized incidence rates were calculated using direct standardization to the World Standard Population [10] in the age categories 0–9, 10–19, 20–29, 30–39, 40–49, 50–59, 60–69 and 70+ years. It was not possible to determine how many cases were not ascertained during this period at the two smaller public hospitals in country centres in the Top End (Nhulunbuy and Katherine); thus the rates cited in this report are minimum incidence rates.

Genetic typing of GAS isolates

Where GAS isolates were available they were characterized using Vir typing, a technique of genetic fingerprinting. The methodology is described elsewhere [11], but briefly it entails amplification of the *mga* regulon of the streptococcal genome by long PCR. The amplified products were then digested with restriction enzymes *Hae*III and *Hin*fI, before size fractionation by agarose gel electrophoresis. The resulting band patterns are then compared against reference strains.

To determine whether the unique M type 1 clone of GAS which has been implicated in the majority of recent severe GAS infections in North America, Europe, New Zealand and Australia [12, 13] was also causing bacteraemia in the Northern Territory, we Vir typed three isolates from a previous study of GAS bacteraemia in Melbourne [13] and compared the resulting Vir type to that of strains in the present study and to the Vir types of strains from other collections in the Northern Territory.

Statistical analyses

Data were analysed using Epi-Info Version 6 (Centers for Disease Control and Prevention, Georgia) and Stata Release 5 (Stata Corporation, Texas). Mean

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values are presented ± standard deviations. Associations between categorical variables were analysed using the χ^2 test or Fisher's exact test, as appropriate. Mean ages of patients were compared using the two sample t test. A critical P value of $< 0{\cdot}05$ was used for all analyses.

This study was approved by the local Institutional Ethics Committee, which includes an Aboriginal Ethics Sub-Committee.

RESULTS

Seventy-two episodes of GAS bacteraemia were identified in 63 patients. Thirty-six patients (57%), with 44 episodes, were Aboriginal Australians. Twenty-seven patients (43%), with 28 episodes, were non-Aboriginal. Of the 61 patients for whom gender was known, 31 were males (51%). Nine repeated episodes occurred in 6 patients, 5 Aboriginal and 1 non-Aboriginal. The annual number of episodes ranged from 9–15.

Aboriginal patients were younger than non-Aboriginal patients. The mean age of 61 patients for whom age was known (at first diagnosis for those with multiple episodes) was 41·7 ± 24·7 years, 32·0 ± 22·2 years for 36 Aboriginal patients and 55·8 ± 21·5 years for 25 non-Aboriginal patients (difference 23·8 years, 95% CI 12·4–35·2). Twenty-nine of 36 Aboriginal patients were aged < 50 years at first diagnosis compared to 9 of 25 non-Aboriginal patients ($\chi^2 = 12{\cdot}5$, $P < 0{\cdot}0001$). Twenty-four of all adults were Aboriginal whereas all 12 children were Aboriginal ($\chi^2 = 10{\cdot}4$, $P = 0{\cdot}001$). Including repeated episodes and where the age was known, 32 of 59 episodes in adults were in Aboriginals, compared to all 12 episodes in children ($\chi^2 = 8{\cdot}9$, $P = 0{\cdot}002$). The age range in children was 7 weeks to 5 years, and five cases (42%) were aged less than 1 year.

Including all 72 episodes the overall crude incidence rate of GAS bacteraemia in the Top End was 9·3 per 100000 per year; 23·8 per 100000 per year in Aboriginal people and 4·7 per 100000 per year in non-Aboriginal people (incidence rate ratio 5·0, 95% CI 3·0–8·4). The age-standardized incidence rate for the 70 episodes where the age was known was 32·2 per 100000 per year in Aboriginal people, and 6·4 per 100000 per year in non-Aboriginal people (incidence rate ratio 5·0, 95% CI 3·3–7·8).

Clinical data were available for 66 cases. At least one risk factor was implicated in 56 of 68 episodes (82%), and over 90% of adults had at least one risk factor compared with 42% of children. Most risk factors were found in a similar proportion of episodes in Aboriginal and non-Aboriginal patients, with the exceptions of chronic renal disease (significantly more common in episodes in Aboriginal patients). When the data were analysed by patient ($n = 59$) instead of by episode ($n = 68$), the association of each risk factor with ethnicity lessened (e.g. 13 of 36 Aboriginal patients (36%) had chronic renal disease compared with 3 or 23 non-Aboriginal patients (13%); $\chi^2 = 3{\cdot}8$, $P = 0{\cdot}073$). Seventy-three percent of adults were smokers, but this was as common among Aboriginal adults (24 of 32, 75%) as among non-Aboriginal adults (17 of 24, 71%).

The most common focus of infection was the skin, whereas there were no cases of pharyngitis (Table 1). Fifty-six percent of episodes were associated with cellulitis, and 37% were associated with skin sores. Cellulitis and skin sores were common in episodes in both Aboriginal and non-Aboriginal patients. However, the pattern of skin sores was different in episodes in Aboriginal compared with non-Aboriginal patients. Ten of 14 episodes with skin sores in Aboriginal patients were associated with impetigo and there were 2 cases of ulcers and 1 each of pressure sores and wound infection whereas impetigo was associated with only 2 of 11 cases with skin sores in non-Aboriginal patients, the remainder being associated with ulcers (6), pressure sores (1), wound infection (1), and boils (1). Scabies was found exclusively in Aboriginal patients, especially children. Eleven of 44 episodes (25%) in Aboriginal patients were associated with scabies but none was in non-Aboriginal patients ($\chi^2 = 7{\cdot}2$, $P = 0{\cdot}006$); and 5 of 12 episodes (42%) in children were associated with scabies compared with 6 of 56 (11%) in adults ($\chi^2 = 7{\cdot}0$, $P = 0{\cdot}008$). Forty episodes (59%) were associated with either cellulitis, scabies or skin sores; 23 were Aboriginal and 17 non-Aboriginal ($\chi^2 = 2{\cdot}2$, $P = 0{\cdot}137$). Twenty-six of 38 episodes (68%) of cellulitis were associated with skin sores or scabies, whereas skin sores or scabies were present in only 2 of 30 episodes where cellulitis was absent ($\chi^2 = 25{\cdot}5$, $P < 0{\cdot}0001$). Skin sores and scabies were each associated with cellulitis ($P < 0{\cdot}0001$ for skin sores and $P = 0{\cdot}001$ for scabies).

Isolated bacteraemia was more common in children than adults, which accounted in part for it being more common in episodes in Aboriginal than in non-Aboriginal patients. There were two cases of necrotizing fasciitis and three cases of soft tissue necrosis. All five necrotizing infections occurred in

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Table 1. *Focus of infection and diagnosis of 68 episodes of GAS bacteraemia in 59 patients*

Feature	Children ($n = 12$)*	Adults ($n = 55$)*	P value†	Aboriginal ($n = 44$)*	Non-Aborig. ($n = 24$)*	P value†
Superficial focus of infection						
Pharyngitis	0	0	—	0	0	—
'Skin sores'‡	5 (42)	20 (36)	0·698	14 (32)	11 (46)	0·252
Other skin focus§	0	4 (7)	1·000	4 (9)	0	0·289
Diagnosis						
Cellulitis	6 (50)	32 (57)	0·651	21 (48)	17 (71)	0·067
Isolated bacteraemia	5 (42)	8 (14)	0·029	11 (25)	2 (8)	0·117
Pneumonia	0	6 (11)	0·581	5 (11)	1 (4)	0·413
Septic arthritis	0	3 (5)	1·000	3 (7)	0	0·548
Post-operative	0	3 (5)	1·000	1 (2)	2 (8)	0·283
Necrotizing fasciitis	0	2 (4)	1·000	1 (2)	1 (4)	1·000
Post-partum	0	2 (4)	1·000	1 (2)	1 (4)	1·000
Osteomyelitis	1 (8)	0	0·176	1 (2)	0	1·000
Urinary infection	0	1 (2)	1·000	0	1 (4)	1·000
Shigellosis	0	1 (2)	1·000	1 (2)	0	1·000

* Numbers in parentheses are percentages.
† Calculated using χ^2 test or Fisher's exact test when appropriate.
‡ Refers to any of impetigo, infected skin ulcers, pressure sores, wound infection or boils.
§ One patient with four repeated episodes had cutaneous calciphylaxis related to end-stage renal failure and dialysis.
‖ The fact that some columns add up to numbers greater than those specified may be attributed to multiple diagnoses for given patients.

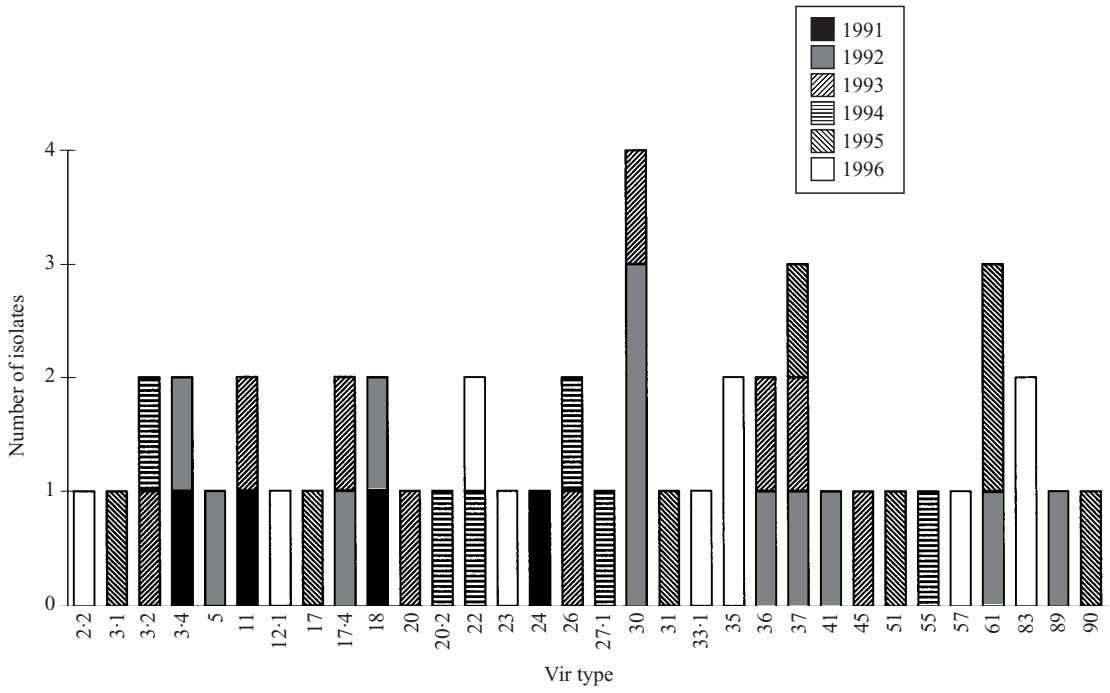

Fig. 1. Vir types of isolates from 50 episodes of GAS bacteraemia, by year of diagnosis.

adults (age range 27–84 years) with multiple risk factors. Three of the five were associated with streptococcal toxic shock syndrome and one died.

Altogether there were 9 deaths (13%) and 7 cases of streptococcal toxic shock syndrome (10%), all in adults, among the 69 episodes of bacteraemia where outcome was known including 9 multiple episodes. Three cases with streptococcal toxic shock syndrome died; all had multiple underlying disorders. There were a further 3 cases with shock, 2 of whom were

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known to have multiple underlying disorders and died of septic shock, but who did not satisfy the criteria for streptococcal toxic shock syndrome. All five patients without streptococcal toxic shock syndrome who died had multiple underlying problems. The mean age at death was 61·7 ± 10·1 years; 56·8 ± 6·9 years for 4 Aboriginal deaths and 65·6 ± 11·2 years for 5 non-Aboriginal deaths (difference 8·8 years, 95% CI −6·3 to 24·0 years). Twenty-one of 69 episodes (30%) were associated with at least one complication, including the 13 patients who died and/or had streptococcal toxic shock syndrome described above. The 9 episodes of repeated bacteraemia in 6 patients occurred an average of 1·5 years after the previous episode (range 2 months–3·9 years); all of these patients had underlying problems, including 3 with chronic renal failure.

Isolates were available for Vir typing from 50 of the 66 episodes. The 50 isolates were of 32 different Vir types, of which the most common Vir type (VT 30) was found in only 4 isolates (8%) (Fig. 1). The Vir types were spread over the duration of the study; only VT 30 showed some evidence of clustering in 1992–3. There was no clustering of VTs with skin-associated infections (cellulitis, skin sores, scabies) or with complicated infections. Of the 21 isolates not associated with skin foci, only 9 were Vir types not also represented in the skin-associated isolates. Isolates from the two necrotizing fasciitis cases were VT 22 and VT 57. Isolates were available for three of those with repeated episodes of bacteraemia and in each case the Vir types were different.

The three M1 isolates which came from the single clone responsible for much of the recent resurgence of invasive disease around the world were VT 78. This Vir type was not found in any of the isolates in patients with bacteraemia in our study. Over 2000 GAS isolates from community and hospital sources in the Northern Territory since 1989 have been Vir typed at the Menzies School of Health Research. VT 78 has been found only three times, always in non-Aboriginal patients, twice from infected wounds and once from a case of sore throat.

DISCUSSION

We found only one other study in which invasive GAS diseases in indigenous and non-indigenous populations were compared [14]. In that study, Native Americans in Arizona were found to have a crude incidence rate of invasive GAS infections of 36·5 per 100000 per year, 11 times higher than the incidence in the rest of the population of the same county. Native Americans were not more likely to have at least one risk factor than patients of other ethnicities, but were more likely to have diabetes or cirrhosis. We found that Aboriginal Australians had a very similar pattern of disease to that in Native Americans. The incidence rate in Aboriginal people was comparable to the Native Americans (crude incidence 23·8 and age-standardized incidence 32·2 per 100000 per year in Aboriginal people; age-standardized incidence in Native Americans was 46·0 per 100000 per year but was standardized to the Arizona population rather than the World Standard Population [14]), and the incidence rate in Aboriginal people was five times that of non-Aboriginal people.

Consistent with the findings of Hoge and colleagues [14] for Native Americans in Arizona we found that, with a few exceptions, non-Aboriginal people with GAS bacteraemia were as likely as Aboriginal people to have risk factors for infection. The proportion of children with risk factors in our study (42%) was similar to that found in other studies [13, 15]. However, over 90% of adult patients in our study also had underlying problems which may have predisposed them to infections, a higher proportion than previously reported [1, 16]. This is at odds with the experience in many countries of invasive GAS infections increasingly affecting previously healthy people.

There was no evidence in our study that particularly virulent strains of GAS caused episodes of bacteraemia; no single strain was isolated from more than a few cases, there was no obvious temporal clustering of cases or of Vir types, and the isolates came mainly from Vir types frequently found in skin swabs performed in Aboriginal communities (unpublished observations). The major (M type 1) clone responsible for many invasive GAS infections elsewhere did not cause any cases of bacteraemia in this study, although this clone has been found to cause skin and pharyngeal infection in three non-Aboriginal people. We found no evidence of the two M types (1 and 3) most commonly identified from invasive infections elsewhere. Recently, sequences of the *emm* gene (the gene for M protein) were found to be concordant with Vir types among isolates from the Northern Territory [17]. The sequences of the *emm* genes for eight of the Vir types in the present report were included in that previous study and a further seven have been sequenced since (unpublished

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results); none of these had the gene for M type 1 or M type 3.

However, it seems likely that a major risk factor for GAS bacteraemia in Aboriginal people in the Northern Territory is high levels of exposure to a wide array of GAS. There are high rates of GAS pyoderma in Aboriginal communities [7], and earlier studies have found up to 14 genetically-distinct strains of GAS circulating in individual communities at a given point in time [18].

The high diversity of strains circulating in the Northern Territory [21] and causing bacteraemia in this study suggests that GAS vaccines which offer type specific protection against the M types which most commonly cause invasive infections in temperate-climate populations may not be efficacious.

Although the risk of invasive GAS infections was greater for Aboriginal than for non-Aboriginal people, the data suggested a degree of protection in Aboriginal adults compared with Aboriginal children; all 12 children with GAS bacteraemia in this series were Aboriginal, compared with 24 of 49 adults ($P = 0{\cdot}001$). This may be due to the development of some immunity as a result of life-long repeated exposure to GAS; levels of opsonic antibodies to GAS carbohydrate increase with age and may account partially for the reduced incidence of GAS infections beyond childhood [19]. This could explain why the relative risk of GAS bacteraemia for Aboriginal compared with non-Aboriginal people in this series (about 5) was so much lower than the relative risk of rheumatic heart disease (46) in the same population [20]; rheumatic heart disease results from acute rheumatic fever during childhood and adolescence, when immunity due to repeated GAS exposure may be less than at older ages.

As in this study, others have found that skin was the most common site of infection, although in most other studies cellulitis and wound infections constituted the majority of skin foci [4, 16]. These infections constituted the majority of skin foci in our non-Aboriginal patients, but impetigo and associated scabies were the most common primary sources in Aboriginal patients, a pattern reported only rarely in other studies. Scabies infestation often underlies impetigo in Aboriginal communities [7], which in turn has been implicated in high rates of acute rheumatic fever and acute post-streptococcal glomerulonephritis [8, 21]. We found no episodes of pharyngitis underlying GAS bacteraemia in children or adults. This is at variance with many previous reports indicating that pharyngitis was an important focus of infection, particularly in children [13, 15, 16]. One US study reported that GAS isolates from sterile sites had genetic arrangements which indicated that they originated from the upper respiratory tract rather than from skin [22], and another used genetic fingerprinting to implicate pharyngeal strains of M types 1 and 3 in many cases of invasive infection [4]. Although we may have missed some cases of asymptomatic or mild pharyngitis, our results are consistent with the low rates of GAS throat carriage found in Aboriginal children in the Northern Territory [7]. In this region, skin rather than throat infections appear to be the major source of exposure to GAS, leading not only to post-streptococcal diseases but also to invasive infections.

The mortality rates in children and adults in our study were comparable with previous studies [1, 13, 15, 16]. Over recent years in many countries severe infections and death have been found increasingly in younger, previously-healthy patients [1, 13, 14]. We found instead that adult patients almost always had risk factors, and that all patients who died or developed streptococcal toxic shock syndrome had multiple underlying problems. The only group of patients with fewer risk factors were children, all Aboriginal, none of whom developed complications of their infections.

In our study there was a substantial group of patients with repeated GAS bacteraemia, a finding which has not been reported elsewhere. All six of these patients had underlying problems, and three had arterio-venous fistulae as likely entry points for organisms. In all five repeated episodes in which isolates were also available from the initial episodes, the Vir types were found to be different, suggesting that these patients were exposed repeatedly to different GAS strains.

In the Northern Territory, severe GAS infections remain largely limited to the traditional at-risk groups, the elderly or people with underlying risk factors. In addition, younger Aboriginal people are at increased risk of GAS bacteraemia, although from our study not of severe complications or mortality. Their increased risk is related mainly to high rates of exposure, particularly through impetigo lesions. This, in turn, reflects the socio-economic disadvantage and overcrowded living conditions in remote Aboriginal communities. There is, as yet, no evidence of a surge in severe invasive GAS infections due to particularly virulent strains that has been seen elsewhere.

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