Effectiveness of Clindamycin and Intravenous Immunoglobulin, and Risk of Disease in Contacts, in Invasive Group A Streptococcal Infections

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(See the Editorial Commentary by Tan and Sriskandan on pages 366–8.)

Background. The use of clindamycin and intravenous immunoglobulin (IVIG) in treatment of invasive group A streptococcal (iGAS) infection, and the need for prophylactic antibiotics in close contacts, remains contentious. Controlled trials are unlikely to be conducted, so prospective, observational studies provide the best data to inform practice.

Methods. We conducted population-based, prospective, active surveillance of iGAS infections throughout the state of Victoria, Australia (population 4.9 million), from March 2002 through August 2004.

Results. Eighty-four cases of severe iGAS infection (streptococcal toxic shock syndrome, necrotizing fasciitis, septic shock, or GAS cellulitis with shock) were identified. Clindamycin-treated patients had more severe disease than clindamycin-untreated patients but lower mortality (15% vs 39%; odds ratio [OR], 0.28; 95% confidence interval [CI], 0.10–0.80). Among those who received concurrent IVIG, the fatality rate was lower still (7%). The adjusted point estimate of the OR for mortality was lower in clindamycin-treated patients (0.31; 95% CI, 0.09–1.12) and clindamycin plus IVIG–treated patients (0.12; 95% CI, 0.01–1.29) compared with clindamycin-untreated patients. Three confirmed cases of iGAS infection occurred in household contacts of index cases. The incidence rate of iGAS disease in contacts was 2011 (95% CI, 413–5929) times higher than the population incidence in Victoria.

Conclusions. Our data suggest that clindamycin treatment of patients with severe iGAS infections substantially reduces mortality and that this effect may be enhanced by concurrent treatment with IVIG. The dramatically increased risk of iGAS disease among household contacts within 1 month of the index case highlights a potential role for antibiotic prophylaxis.

Keywords. streptococcal; clindamycin; immunoglobulin; contact; mortality.

There has been an increase in the incidence and severity of invasive group A streptococcal (iGAS) infections in many industrialized countries over the past 3 decades [1–3]. Three issues relating to the management of these infections remain contentious: whether the addition of clindamycin to a β-lactam antibiotic improves outcomes; whether intravenous immune globulin (IVIG) improves outcomes; and whether there is a role for antibiotic prophylaxis in close contacts of cases.

Clindamycin is currently widely recommended for use in addition to a β-lactam antibiotic for severe iGAS infections, although opinions vary as to whether it should be restricted to cases of streptococcal toxic shock syndrome (STSS) [4–6]. The evidence supporting
its use is based mainly on animal data and in vitro studies [7, 8]. In vivo studies confirm that clindamycin, particularly if administered after early-log-phase growth, inhibits transcription and production of a range of streptococcal proteins, including pyrogenic exotoxin superantigens [9–12]. Evidence of clinical benefit in humans is limited to retrospective case series [13, 14].

The definitive study of IVIG for iGAS infections—a placebo-controlled, randomized trial in STSS—was prematurely terminated because of slow enrollment [15]. There was a trend to reduced mortality, significantly reduced sepsis-related organ failure assessment scores at days 2 and 3, and significantly increased ability of plasma to neutralize superantigens in the IVIG-treated group. A number of other observational studies suggest that IVIG may reduce mortality or improve outcome in STSS with or without necrotizing fasciitis (NF) [16, 17], although one retrospective study failed to find benefit in STSS [18]. In addition, there are many animal and in vitro studies documenting the potential modes of action and biological plausibility for benefit of IVIG [12, 19, 20].

Invasive GAS disease has been well documented to occur in close contacts of patients [21]. Antibiotic treatment of close contacts of people with severe iGAS disease is routinely recommended in Canada [22], based on surveillance finding that the attack rate in household contacts was almost 200 times the yearly incidence in the wider population [23]. By contrast, routine prophylaxis is not recommended in the United States and only occurs in specific circumstances in the United Kingdom [24]. Surveillance of >12 million people over a period 2.5 years in several US states detected an attack rate in contacts of 66 per 100 000 compared with the annual incidence of sporadic disease of 3.5 per 100 000 [25]. Unpublished surveillance data from the United Kingdom found that >2000 close contacts would need treatment to prevent 1 case, assuming 100% effectiveness of prophylaxis [26].

The rarity of iGAS disease means that randomized controlled trials of unproven management strategies would have to be large, multicenter, complex, and expensive. The premature termination of the European IVIG trial makes it unlikely that similar trials will be attempted in the foreseeable future. Therefore, the most reliable evidence will come from detailed prospective observational studies that attempt to control for confounding factors.

We conducted prospective, enhanced surveillance of iGAS disease in one state of Australia over 2.5 years [27], and took the opportunity to determine if there was evidence for the effectiveness of clindamycin or IVIG, and to document the risk of iGAS disease in household contacts of cases.

METHODS

Our case ascertainment methodology has been previously reported [27]. In brief, we conducted active, prospective, statewide surveillance for iGAS infections in the state of Victoria, Australia, between 1 March 2002 and 31 August 2004. The population under surveillance was 4.9 million according to census figures from the Australian Bureau of Statistics.

We established a network of 63 laboratories, 45 hospitals, and general practitioners. In addition to passive reporting, laboratories were contacted twice per month. We reviewed hospital discharge datasets from all Victorian hospitals with an intensive care unit or >200-bed capacity (n = 45 in 2001) every 3 months for International Classification of Diseases, Tenth Revision (ICD-10) codes indicating GAS disease. Detailed demographic and clinical data for all patients were collected from the treating physician and/or by medical record review.

Case Definitions

Confirmed cases were defined as one of the following:

(a) the isolation of GAS from a normally sterile site (blood, cerebrospinal fluid, or other sterile fluid/tissue);
(b) a clinical presentation of necrotizing fasciitis with evidence of GAS infection (culture of GAS or the presence of gram-positive cocci from tissue specimen or wound swab or positive streptococcal serology);
(c) a clinical presentation of pharyngeal abscess (quinsy) requiring hospitalization and parenteral antibiotics accompanied by the isolation of GAS from a throat swab.

Severe iGAS infection was defined a priori as any of the following: STSS (defined according to published criteria [28]), NF, septic shock, or severe cellulitis (cellulitis with hypotension and evidence of GAS infection) (Table 1). These definitions were applied by the investigators (rather than the treating clinicians) using comprehensive data information collected on the Data Collection Form.

Clindamycin and IVIG Study

Data were collected on treatments and outcomes for all cases of severe iGAS disease. Patient characteristics were compared using the Wilcoxon rank-sum test for continuous variables and the χ² test, or Fisher exact test where appropriate. Univariate and multivariate logistic regression were performed to generate odds ratios to assess the effect of treatment on survival, using the case fatality rate at 30 days as the outcome. Our primary analysis assessed the effect of any clindamycin treatment. In a secondary analysis, the clindamycin treatment group was subdivided into those who did or did not also receive IVIG. Confounders included in the multivariate models were presence of STSS and age, which was categorized as ≥60 years (because 86% of case fatalities were in this older age group). We separately included hospital type (one of the 6 major Melbourne metropolitan teaching hospitals or any other hospital) as a variable to determine any additional influence of this factor. To determine if there was a differential impact of treatment on
outcome based on disease severity, we separately ran an age-adjusted regression on the subset of 58 patients with STSS, NF, or both. Because of small numbers, we aimed to limit the number of variables included in the regression analysis. Potential confounders not included in our analyses were NF (as all but 1 NF patient received clindamycin), and presence of chronic underlying health conditions (the prevalence did not differ between the clindamycin and non-clindamycin treatment groups).

### Household Contact Study

We excluded index cases of iGAS disease in patients who were institutionalized. Secondary cases were actively identified and recorded by trained surveillance staff. The interval between disease onset (estimated as the date of hospital admission) in an index case and disease onset in the corresponding secondary case was determined, as were the eDNA-types for each case-pair/cluster.

The number of household contacts for each iGAS case was collected retrospectively in 2005 via postal questionnaire to each noninstitutionalized index case who had provided consent for detailed data collection, had not died during the study period and had a known postal address. The questionnaire sought information regarding the number of household contacts the index case had at the onset of iGAS disease. Nonresponders were contacted by telephone to improve ascertainment.

Demographic characteristics of responders were compared with those of nonresponders. After establishing that survey respondents appeared to be representative of all iGAS cases, we then estimated the total number of household contacts for all patients by extrapolating from the average number of household contacts per survey respondent.

The attack rate (secondary cases per 100 000 person-years at risk) for iGAS disease among household contacts was calculated assuming a 30-day at-risk period from disease onset in the index case. The risk among household contacts compared with the general population was calculated as an incidence rate ratio (IRR) using the estimated background annual incidence of all
confirmed sporadic iGAS disease in Victoria determined during our study [27]. Because of the low number of infections among household contacts, exact confidence intervals (CIs) for IRR estimates were calculated.

Analyses were performed using Stata software version 12 (StataCorp, College Station, Texas).

Ethics

The study was approved by the Victorian Department of Human Services’ Ethics in Human Research Committee and by >70 individual health service ethics committees.

RESULTS

There were 333 confirmed cases of iGAS disease identified over the 2.5-year study period (annual incidence, 2.7 per 100 000 [95% CI, 2.4–3.0]). Among these 333 cases, 84 met the definition for severe iGAS disease.

Usage and Effectiveness of Clindamycin and IVIG

Of the 84 patients with severe iGAS disease, 53 were admitted to a major teaching hospital. Clindamycin was used in 53 (63%) cases and IVIG was used in 14 (17%). All patients treated with IVIG were also treated with clindamycin (Table 2).

More patients admitted to a teaching hospital were treated with clindamycin than those admitted to any other hospital (75% vs 45%, P = .009), and also more were treated with IVIG, although this difference was not significant (21% vs 10%; P = .236).

Clindamycin-treated patients were younger and had more severe disease than clindamycin-untreated patients, as measured by presence of STSS, length of hospital stay, and admission to the intensive care unit (ICU) (Table 3). There was a significant association between clindamycin treatment (with or without IVIG) and reduced case fatality rate in univariate analysis (15% vs 39%; P = .014; odds ratio [OR], 0.28 [95% CI, .10–.80]; Table 4). Multivariate logistic regression, adjusted for age and the presence of STSS, was still suggestive of this association (OR, 0.31 [95% CI, .09–1.12]; Table 4). When we added type of hospital to the

| Table 2. Clinical Manifestations and Treatment of 84 Patients With Severe Invasive Group A Streptococcal Disease |
| --- | --- | --- |
| Manifestation | No. of Patients | Treated With Clindamycin (%) | Treated With IVIG (%) |
| NF + STSS | 20 | 20 (100) | 7 (35) |
| NF + septic shock | 1 | 1 (100) | 0 |
| NF alone | 8 | 7 (88) | 1 (13) |
| STSS alone | 29 | 17 (59) | 6 (21) |
| Septic shock alone | 16 | 6 (38) | 0 |
| Severe cellulitis | 10 | 2 (20) | 0 |
| Total severe iGAS | 84 | 53 (63) | 14 (17) |

Abbreviations: iGAS, invasive group A Streptococcus; IVIG, intravenous immunoglobulin; NF, necrotizing fasciitis; STSS, streptococcal toxic shock syndrome.

Table 3. Characteristics of 84 Patients With Severe Invasive Group A Streptococcal Disease

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Treated With Clindamycin (%)</th>
<th>Clindamycin Untreated (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics of hospital admission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVIG treatment</td>
<td>14/52 (27)</td>
<td>0/31 (0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ICU admissions</td>
<td>39/53 (73)</td>
<td>9/30 (30)</td>
<td>.001</td>
</tr>
<tr>
<td>Length of stay, d, median (range)</td>
<td>20.0 (6–131)</td>
<td>10.5 (3–50)</td>
<td>.020</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death at 30 d</td>
<td>8/53 (15)</td>
<td>12/31 (39)</td>
<td>.014</td>
</tr>
</tbody>
</table>

Denominators indicate number for which information is available.

Abbreviations: ICU, intensive care unit; IVIG, intravenous immunoglobulin; NF, necrotizing fasciitis; STSS, streptococcal toxic shock syndrome.

* Chronic conditions: any of asthma, chronic bronchitis, chronic heart failure, coronary artery disease, renal failure, nephritic syndrome, chronic hepatitis, chronic hematological disease, diabetes mellitus.

Table 4. Odds Ratios for Risk of Death Predicted by Clindamycin Treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Univariate OR</th>
<th>95% CI</th>
<th>Multivariate OR*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clindamycin vs no clindamycin</td>
<td>0.28</td>
<td>.10–.80</td>
<td>0.31</td>
<td>.09–1.12</td>
</tr>
<tr>
<td>Clindamycin without IVG vs no clindamycin</td>
<td>0.35</td>
<td>.12–1.03</td>
<td>0.39</td>
<td>.10–1.46</td>
</tr>
<tr>
<td>Clindamycin with IVG vs no clindamycin</td>
<td>0.12</td>
<td>.01–1.05</td>
<td>0.12</td>
<td>.01–1.29</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; IVIG, intravenous immunoglobulin; OR, odds ratio.

* Models adjusted for presence of streptococcal toxic shock syndrome and age ≥60 years.
regression (major metropolitan teaching hospital or other), this had minimal impact on the result (OR, 0.32 [95% CI, .08–1.22]). To determine if there was an effect of ICU admission independent of hospital type, we included ICU admission but excluded hospital type, and there was also minimal impact on the result (OR, 0.28 [95% CI, .07–1.11]). There was also minimal impact when we looked just at the subset of patients who had STSS, NF, or both (OR, 0.33 [95% CI, .08–1.40]).

When clindamycin-treated patients were divided into those who received clindamycin without IVIG and those who received clindamycin and IVIG, we found that IVIG-treated patients were less likely to be immunocompromised (0% vs 25%) or to have underlying chronic conditions (29% vs 71%) and more likely to have STSS (93% vs 61%). Mortality in those treated with clindamycin and IVIG was 7% (1 of 14) compared with 18% (7 of 39) in those treated with clindamycin without IVIG (P = .24). After adjusting for age and the presence of STSS, we found that treatment with clindamycin together with IVIG was suggestive of a lower case fatality rate, but the association was not statistically significant (adjusted OR, 0.12 [95% CI, .01–1.29]) compared with clindamycin without IVIG (adjusted OR, 0.39 [95% CI, .10–1.46]).

Risk of iGAS Disease in Household Contacts
There were 3 confirmed secondary cases in household contacts of people with iGAS disease. All occurred within 8 days of the index case (Table 5). An additional 3 cases occurred in (nonhousehold) close contacts—1 occurred in a coresident of hostel accommodation (but the infecting strains were of different emm types), and another 2 patients were resident in the same nursing home ward as the index case. These patients were excluded from further analysis because they were institutionalized.

Estimate of Number of Household Contacts at Risk
Of the 333 confirmed patients, 79 were institutionalized and 3 were secondary cases, leaving 251 noninstitutionalized index cases. Of these, 127 met our criteria to be sent questionnaires. Ten questionnaires were returned as a result of incorrect addresses, leaving 117 valid questionnaires mailed out. Ninety-five responses were received (response rate, 81%). The 95 responders were compared with the 156 other noninstitutionalized index cases: there were no significant differences between these groups in mean age (41.6 years vs 46.2 years; P = .151), sex (57% male vs 49%; P = .230), or place of residence (74% vs 74%; P = .921).

There were a total of 253 household contacts for the 95 responders (mean, 2.66 per household; median 2; range, 0–12). As there were 251 confirmed noninstitutionalized cases, we estimated the total number of household contacts for these cases to be 668 (251 × 2.66). There were 3 secondary cases of iGAS disease in these estimated 668 contacts, which equates to an attack rate of 5468 secondary cases per 100 000 person-years at risk, assuming an at-risk period of 30 days after the index case. Comparing this attack rate with the 30-day incidence in the Victorian general population gives an IRR of 2011 (95% CI, 413–5929).

DISCUSSION
The results from this observational study suggest that the use of clindamycin in severe iGAS disease is associated with reduced mortality and that concurrent treatment with IVIG enhances this protective effect. It also highlights the dramatically increased risk of iGAS disease in household contacts of cases. Patients with severe iGAS disease who received clindamycin were half as likely to die despite having more severe disease as measured by the presence of STSS or necrotizing fasciitis, admission to an intensive care unit, or length of stay. The fatality rate was lower still in the patients who were also treated with IVIG. After adjusting for confounders, the 30-day fatality ORs for treatment with clindamycin or for treatment with clindamycin and IVIG were substantially below 1. However, due to the unavoidably low number of cases, this failed to reach statistical significance. We did not find that the association between

Table 5. Summary of Index and Contact Cases of Invasive Group A Streptococcal Disease

<table>
<thead>
<tr>
<th>Case-Pair No.</th>
<th>Case Status</th>
<th>Sex</th>
<th>Age, y</th>
<th>Interval From Index Case, d</th>
<th>Diagnosis</th>
<th>emm Type</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Index</td>
<td>M</td>
<td>39</td>
<td>. . .</td>
<td>STSS, NF</td>
<td>1</td>
<td>Survived</td>
</tr>
<tr>
<td>1</td>
<td>Secondary</td>
<td>F</td>
<td>9</td>
<td>1</td>
<td>Septic arthritis</td>
<td>1</td>
<td>Survived</td>
</tr>
<tr>
<td>2</td>
<td>Index</td>
<td>F</td>
<td>58</td>
<td>. . .</td>
<td>Unknown</td>
<td>89</td>
<td>Died</td>
</tr>
<tr>
<td>2</td>
<td>Secondary</td>
<td>F</td>
<td>0.2</td>
<td>8</td>
<td>Peritonitis</td>
<td>89</td>
<td>Survived</td>
</tr>
<tr>
<td>3</td>
<td>Index</td>
<td>F</td>
<td>80</td>
<td>. . .</td>
<td>STSS, NF</td>
<td>1</td>
<td>Died</td>
</tr>
<tr>
<td>3</td>
<td>Secondary</td>
<td>F</td>
<td>92</td>
<td>6</td>
<td>Cellulitis</td>
<td>a</td>
<td>Survived</td>
</tr>
</tbody>
</table>

Abbreviations: NF, necrotizing fasciitis; STSS, streptococcal toxic shock syndrome.

* Isolate not available for typing.
clindamycin treatment and mortality was affected either by treatment in a major teaching hospital or disease severity (the association remaining almost identical when just the subset of cases with STSS or NF was analyzed). We did not collect sufficient data on timing of death to determine whether the patients who died but also received clindamycin and/or IVIG could have been expected to benefit from this treatment.

Together with the in vitro and animal study evidence for its effectiveness, as well as other observational study findings, these data support a recommendation that clindamycin should be used in addition to β-lactam antibiotics in severe iGAS disease regardless of the presence or absence of STSS. Until further studies provide more evidence as to which patients will benefit from clindamycin, we suggest that clindamycin should be added to the treatment in severe iGAS disease (STSS, NF, septic shock, or cellulitis with hypotension and evidence of GAS infection) may be an appropriate basis for clinical guidelines.

We were unable to provide convincing data on any potential benefits of IVIG, although the reduction in the point estimate of mortality when IVIG was used in addition to clindamycin supports the limited existing data suggesting a role for IVIG in severe iGAS disease. The exception is a multicenter retrospective study [18], which failed to document reduced mortality in children treated with IVIG for STSS, but the overall mortality rate in that study was only 4.2%, lower than the mortality in STSS patients in our study (23% overall, 8% in children) [27]. This raises the possibility that any benefits of IVIG may be more apparent in those with more severe disease and/or adults, but more evidence is needed.

We found that household contacts of iGAS cases were at >2000 times increased risk of iGAS disease themselves than the general population. Our data suggest that, in the 30 days following onset of disease in the index case, approximately 1 in every 220 household contacts will develop iGAS disease, compared with a risk in the general population of approximately 1 in 500 000. The increased risk for household contacts is likely to be higher, as all cases in contacts occurred within 8 days (although 1 case in the Ontario study occurred 21 days after the index case [23]). We determined the household contacts at risk retrospectively, which raises the possibility of recall bias. However, we believe this is unlikely to have been substantial, given the dramatic impact of iGAS disease on patients and families. A further limitation was our extrapolation of data from 95 responding household contacts to the remaining 156 nonresponders, even though we found no significant differences between these groups on a number of demographic variables. This extrapolation may have introduced imprecision, which we can quantify: Based on the 95 responders, the upper 95% confidence limit for the "true" number of contacts per household (assuming a Poisson distribution) is 3.01. Therefore, the total number of contacts could be as high as 95 x 2.66 (observed) + 156 x 3.01 (unobserved) = 722, compared with our estimated 668. This would reduce our estimate of the IRR from 2011 to 2011 x (668/722) = 1861, which is still much higher than that reported in the 2 other population-based studies discussed below.

There have been 2 other population-based studies addressing the risk of iGAS disease in household contacts (Table 6). The increased risk in our study was substantially greater than those from both the Ontario and US studies, although the calculated risk from those studies for household contacts within 30 days of the index case was still >1400 and >200 times, respectively, than for the general population.

It is not known if this increased risk can be reduced by providing prophylactic antibiotics to household contacts, in the hope of eradicating carriage or treating early infection. Penicillin prophylaxis is effective in the prevention of recurrent cellulitis, giving some encouragement that antibiotic prophylaxis may prevent severe streptococcal infections [29]. Despite this uncertainty, given the rarity, severity and high case fatality

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**Table 6. Summary of Studies of Invasive Group A Streptococcal Disease Risk in Household Contacts of Index Cases**

<table>
<thead>
<tr>
<th>Location, Year</th>
<th>Population, Millions</th>
<th>Surveillance Period, y</th>
<th>Background Annual Incidence (a)</th>
<th>No. of Cases in Contacts</th>
<th>Attack Rate in Contacts (b)</th>
<th>IRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ontario, 1992–1993</td>
<td>10.7</td>
<td>3.5</td>
<td>2.4</td>
<td>4</td>
<td>3581</td>
<td>1492 (405–3837)</td>
</tr>
<tr>
<td>US(a, 1997–1999</td>
<td>12.1</td>
<td>2.4</td>
<td>3.5</td>
<td>1</td>
<td>804</td>
<td>229 (6–1277)</td>
</tr>
<tr>
<td>Victoria, 2002–2004 (present study)</td>
<td>4.9</td>
<td>2.5</td>
<td>2.7</td>
<td>3</td>
<td>5468</td>
<td>2011 (413–5929)</td>
</tr>
</tbody>
</table>

Ontario and US incidence rates taken from updated published data [25].
Abbreviations: CI, confidence interval; IRR, incidence rate ratio.

(a) Per 100 000 person-years at risk.
(b) Assuming a 30-day at-risk period (inferred from published data for Ontario and US studies).
(c) Exact CIs calculated.
(d) Conducted across several states, including Connecticut, Minnesota, California, and Oregon.
rate of iGAS disease, we believe that antibiotic prophylaxis is warranted for household contacts and poses little risk from the use of additional antibiotics. Based on the Victorian data, there are approximately 570 cases of iGAS disease per year in Australia. As the average Australian household has 2.6 occupants [30] we estimate an average of 1.6 household contacts per case. Assuming 100% effectiveness, this would entail offering antibiotics to approximately 912 contacts per year to prevent 4 secondary cases. The choice of antibiotic to be used for prophylaxis has been reviewed by others [24, 25]. Regimens should be used that have a high likelihood of eradicating GAS carriage.

The latest guidelines from Canada recommend restricting antibiotic prophylaxis to household contacts of index cases with particularly severe disease [22]. While iGAS disease, in particular NF, tends to be caused by a limited number of GAS emm-types, this is not universal [31], so we advocate that prophylaxis should not be based on the severity of the index case.

In conclusion, these data suggest that broadening the indications and instituting measures to increase the use of clindamycin and IVIG in iGAS disease may reduce mortality, and that there is a strong case for routine antibiotic prophylaxis for household contacts of cases.

Notes

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