

Group C and G Streptococci Infections: Emerging Challenges

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New reports of serious complications from Group C (GCS) and Group G streptococci (GGS) with probable respiratory entry have been described. Particularly interesting are cases of toxic shock-like syndrome and rheumatic fever in previously healthy patients. Serious GCS and GGS infections will be missed where selective methods for group A streptococci (GAS) only are used on throat specimens.

ABBREVIATIONS: ASO = anti-streptolysin O; BAP = blood agar plate; GAS = group A streptococci; GCS = group C streptococci; GGS = group G streptococci; OIA = optical immunoassay.

INDEX TERMS: streptococcus infections.

Clin Lab Sci 2003;16(4):209

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Group A streptococci (GAS) are considered the primary pathogenic β -hemolytic streptococci cultured from the throat.¹ GAS throat infections are routinely treated to reduce spread to patient contacts, and to reduce suppurative and non-suppurative complications. Standard protocol is to screen with a rapid test for GAS and perform throat cultures on specimens with negative screening results.² New, rapid,

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highly sensitive and specific screening methods have been developed to detect GAS, e.g., optical immunoassay (OIA) by BioStar and DNA probe hybridization by Gen-Probe.³⁻⁵ Therefore, recommendations have been made to replace the standard protocol with these screening methods.⁶⁻⁹ These recommendations are based on the assumption that GAS is the only dangerous streptococcal pathogen that may invade the throat.

Although GAS are the most frequent streptococci isolated from throat cultures, β -hemolytic GCS and GGS and hemolysin deficient variants cause epidemics of exudative pharyngitis/pharyngotonsillitis.¹⁰⁻¹⁶ The rate of positive throat cultures that are GCS rather than GAS positive in certain seasons and geographical areas ranges from 1% to 11%.¹⁶ In addition, GCS and GGS are implicated as a cause of serious complications including rheumatic fever in previously healthy children and adults.¹⁷⁻²⁸ Notably, pharyngeal carriage of GGS and/or GCS and not GAS preceded several rheumatic fever cases.²² The main focus of this paper is the serious complications and sequelae from GCS and GGS in previously healthy adults with confirmed or probable respiratory entry. A patient's quality of life may be permanently impaired because of clinical practices that ignore GCS and GGS unless the specimen comes from a normally sterile site.

LABORATORY DIAGNOSIS OF GAS, GCS, AND GGS
 Standard practice for patients with pharyngitis or pharyngotonsillitis is to obtain a throat swab, then either culture for GAS directly or screen for GAS by a rapid test method and perform throat cultures on the negative GAS screens.^{29,30} Throat specimens are cultured on trypticase soy agar with 5% sheep blood (BAP) at 35 °C overnight in aerobic conditions, and β -hemolytic colonies are subcultured onto fresh 5% BAP with a 0.04U Bacitracin disk. Bacitracin sensitive streptococci in throat specimens are reported as presumptively GAS because 95% of GAS are sensitive and only 9% of non-GAS are sensitive.³¹ Bacitracin sensitivity and β -hemolysis are seen with up to 6% of the GCS isolates and 8% to over 50% of specific GGS isolates.³²⁻³³ Whether Bacitracin sensitive or resistant, GCS and GGS are potential pathogens and yet, are not routinely identified from throat specimens.

The diagnosis of streptococcal throat infections is based on a wide variety of approaches throughout the U.S. Some pediatricians only screen for GAS with rapid tests, some only do cultures, others screen and backup with culture, a few do both, and a few neither.²⁹ Illustrating differences within one small region, survey results from six microbiology laboratories in Northern Illinois showed that in 2001, most laboratories do direct antigen testing for only GAS. Although not routinely performed anymore, when throat specimens are streaked onto BAP, most of these laboratories are reporting non-GAS if they are present in significant numbers. These non-GAS infections are not usually speciated or grouped. Only two laboratories reported further grouping non-GAS.

When more serious complications occur, testing includes a wide variety of protocols. For specimens from sterile sites, preliminary serological or biochemical testing for -hemolytic strep-

tococci includes grouping the C antigen on the surface of the organism or biochemical testing. Agglutination tests may be performed to identify the Lancefield group as one of A-G. Biochemical testing to confirm group A includes bacitracin sensitivity, sulfamethoxazole-trimethoprim (SXT), or pyrrolidonyl-naphthylamide (PYR) hydrolysis. PYR has been shown to be the most specific and sensitive if used alone.³¹ Table 1 contains biochemical reactions used to differentiate group A, C, and G -hemolytic streptococci.

-hemolytic GCS streptococci include *S. equi*, *S. equisimilis*, and *S. zooepidemicus*. With the exception of *S. zooepidemicus*, GCS strains produce hemolysins that cross-react with streptolysins produced by GAS.³⁴ Patients infected with *S. equi* or *S. equisimilis* often have significant ASO titers, and both organisms can be bacitracin sensitive. Lancefield grouping is the best method to definitely identify the organism as group A, C, or G.

GGS streptococci are β-hemolytic, bacitracin resistant (like most group B), or sensitive (like group A), and sodium hippurate positive (like group B). Thus, they may resemble group B or group A, depending upon the biochemical tests used. In addition, the M protein of GGS or GCS matches those of particular strains of group A streptococci that cause rheumatic fever.²² The M protein is a part of the pili, which is a potent virulence factor that resists phagocytosis.³⁵ GGS also have a cross-reactive streptolysin O, so ASO and DNase B titers can rise as a result of GGS infections.^{20,34}

DISCUSSION

Serious complications of GCS and GGS infections

Cases of exudative pharyngitis from GCS and GGS are now being recognized in specific regions of the U.S. and in other countries.¹⁰⁻¹⁶ Sequelae and serious complications once believed to be exclusively from GAS are now confirmed to be from GCS or GGS streptococci.¹⁷⁻²⁸ These groups of streptococci are inhabitants of horses, cows, swine, sheep, foxes, goats, and guinea pigs, and can cause abscesses, septicemia, and pneumonia in these animals.³⁶ Patients who are exposed to farm animals, zoo animals, or unpasteurized milk products are at increased risk for GCS or GGS.

Of the GCS streptococci, *S. zooepidemicus* is considered the most virulent. It has led to the most severe complications in previously healthy people in the past. For instance, five members of a farming family developed pharyngitis due to *S. zooepidemicus*. Three of these patients developed post-streptococcal glomerulonephritis.³⁷ Anti-streptolysin O (ASO) titers were done on serum from the family and the results were nega-

Table 1. Biochemical reactions of -hemolytic group A, C, and G streptococci

Organism	Baci*	SXT†	PYR‡	Sorb§	Treh ⁺
<i>S. pyogenes</i> (gr A)	S (99%)	R	P	N	P
<i>S. anginosus</i> (gr G)	R (99%)	S	N	N	P
<i>S. equi</i> (gr C)	S (80%)	S	N	N	N
<i>S. equisimilis</i> (gr C)	R (99%)	S	N	N	P
<i>S. zooepidemicus</i> (gr C)	S (71%)	S	N	P	N

* Baci = bacitracin

† SXT = sulfamethoxazole-trimethoprim

‡ PYR = pyrrolidonyl arylamidase

§ Sorb = sorbitol

+Treh = trehalose

S = sensitive

R = resistant

N = negative

P = positive

tive. (*S. zooepidemicus* produces a soluble hemolysin, which does NOT cross-react with the hemolysins of GAS.) In another outbreak of pharyngitis (85 patients), *S. zooepidemicus* infection resulted from the ingestion of raw dairy products. Thirty-three percent of these patients developed glomerulonephritis. Certain strains of *S. zooepidemicus* can produce endstreptosin (ESS), a cytoplasmic polypeptide associated with nephritogenic strains of group A streptococci.³⁷

Serious infections and complications from GCS and GGS have been reviewed in papers published from 1979 to present.^{22,36,38-41} GCS and GGS with nephritogenic or rheumatogenic M types homologous with GAS have been identified.^{22,42-44} GCS and GGS are described in reviews as also the cause of serious infections in compromised patients including toxic shock-like syndrome, necrotizing fasciitis, exophthalmitis, puerperal fever, pharyngitis, epiglottitis, pneumonia, impetigo, cellulitis, empyema, septicemia, endocarditis, septic arthritis, osteomyelitis, abscesses, and meningitis (Table 2).^{36,38-41} Cases of young healthy adults and children with life threatening toxic shock-like syndrome, meningitis, and septicemia or sequelae from GCS or GGS are changing the previous paradigm.¹⁷⁻²⁸ These organisms can no longer be considered benign for healthy individuals.

Therapy

Rapid diagnosis of GAS infections is important because of the serious sequelae, including the rheumatic fever and glomerulonephritis that may develop. Rheumatic fever is prevent-

able by early treatment of the initial pharyngeal infection. Although glomerulonephritis is not preventable, early intervention may prevent kidney failure.⁴⁵ Rapid diagnosis of GCS and GGS infections that lead to glomerulonephritis, toxic shock-like syndrome, and rheumatic fever may also prevent unnecessary death and disability. Treatment depends upon the nature and severity of the GCS or GGS infection.

GCS and GGS do not respond as readily to penicillin G as GAS and are more likely to be resistant to penicillin and vary with resistance to erythromycin and other antimicrobials.⁴⁷⁻⁵³ GCS and GGS may be bacitracin sensitive or resistant and both appear to be sensitive to penicillin in vitro; however, in vivo the response is often delayed, and other drugs (especially aminoglycosides) are recommended to effect a cure.⁵³ Penicillin tolerance by GCS and GGS is on the rise. Current literature recommends a combination of penicillin G and gentamicin (aminoglycoside) or other antimicrobials for serious GCS streptococcus infections.⁴⁷⁻⁵³

This in vivo delayed therapeutic response to penicillin in GCS and GGS is in direct contrast to the quite likely immediate in vivo response of GAS to this drug. Therefore, Lancefield grouping of clinical isolates could potentially decrease morbidity in those patients with infections due to GCS or GGS who require more than penicillin in order to recover. GCS infections appear to follow certain patterns. In the past, the most common outcome of GCS infections treated with penicillin G is that the patient recovers from the initial pharyngitis or pyoderma. About a third of patients with pharyngitis infections by nephritogenic strains develop glomerulonephritis.^{37,43} Septicemia, endocarditis, toxic shock-like syndrome, and meningitis are all serious complications of GCS and GGS infections that are frequently fatal. With the increase in penicillin tolerance or resistance and erythromycin resistance in GCS and GGS infections, an increase in serious complications is likely. Pharyngitis will be treated only if it is due to GAS by current protocols of diagnosing pharyngitis. The most frequently prescribed drug for GAS is penicillin. Therefore, a change of practice to rapid identification of the GCS or GGS and the initiation of dual therapy despite extreme in vitro sensitivity to penicillin alone, should improve the recovery chances of these patients.⁵³

CONCLUSIONS

GAS, GCS, and GGS have been reported as transient inhabitants of healthy throats.¹² Evidence of throat carriage of rheumatogenic strains of GCS and GGS may indicate that carriage is not benign. Reports of healthy children and adults

Table 2. Infections, complications, and sequelae caused by GCS or GGS

Initial infection with potential sequelae

Pharyngitis

Sequelae

Glomerulonephritis	Rheumatic fever
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Other infections and complications

Abscesses	Nephritic syndrome
Cellulitis	Osteomyelitis
Empyema	Otitis media
Endocarditis	Puerperal fever
Epiglottitis	Pneumonia
Exophthalmitis	Septic arthritis
Impetigo	Septicemia
Meningitis	Toxic shock-like syndrome
Necrotizing fasciitis	

contracting life-threatening GCS or GGS infections with oral or respiratory entry (confirmed or suspected) suggests that throat specimen screening for GAS may be insufficient for certain populations.

In a recent case, throat cultures on a previously healthy woman were reported as having -hemolytic colonies that were not group A streptococci.⁵⁴ She was not treated. The patient developed bacteremia and meningitis a few days later and *S. zooepidemicus* was isolated from her cerebrospinal fluid. She was then asked if she had unusual pets and reported having goats. Her neural function appears to be permanently impaired. Perhaps, she would be healthy if her throat culture results had been taken seriously.

Replacement of throat cultures with GAS antigen screening or DNA hybridization tests should be reconsidered especially in clinics serving rural communities or areas known to have higher rates of GGS or GCS throat infections. Instead, throat cultures from farmers, veterinarians, rural patients, and known endemic populations should be actively tested for GCS and GGS by Lancefield agglutination tests or other antigen specific test when suspicious colonies appear on BAPs. To assure that each patient is provided the best chance of correct diagnosis and therapy, the following protocol is recommended:

1. screen for GAS with highly sensitive and specific rapid test methods;
2. culture negative screens and collect data for a region to determine rate of positives for GAS, GCS and GGS;
3. if throat infections and serious complications, presumably from GAS, GCS and GGS are missed by the rapid antigen tests, continue BAP cultures of throat specimens;
4. treat GCS and GGS as potentially as pathogenic GAS;
5. in addition to asking about exposures to humans with infections, also ask patients for information on exposure to zoo or farm animals or unpasteurized milk products;
6. speciate the infectious organism when the answer is yes;
7. do antimicrobial susceptibility testing for GCS or GGS infections and treat more aggressively for GGS or GCS especially when *S. zooepidemicus* found.

When infections are positive for GCS or GGS, antibiotics will help prevent life threatening complications. For specific populations, replacing standard throat cultures as a method of identifying throat pathogens with antigen based tests or selective agar cultures that only identify GAS, leaves patients

at risk of being misdiagnosed or undiagnosed resulting in treatment delays.

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