Viridans Streptococci: Friends or Foes?

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"There are in fact two things, science and opinion; the former begets knowledge, the latter ignorance."

— Hippocrates
Overview

• Introduction to the group
• Current taxonomy
• Clinical significance & infections
• Emerging antibiotic resistance
• The role of the clinical microbiology laboratory
Introduction

• Viridans streptococci
  – (Latin). Viridis: green
  – (Greek). Strepto: bent or twisted like a chain
  – (Greek). Kokkos: berry
Introduction

• Viridans Group Streptococci
  – Heterogeneous group of organisms
  – Human commensals
  – Pathogens
Microbiology of the VGS
Microbiology

• VGS generally not beta-hemolytic
  – They may be non-hemolytic
  – Many produce alpha-hemolysis and a greenish discoloration on blood agar plates

• VGS generally do not react with Lancefield grouping sera
Microbiology

• Exceptions
  – *Streptococcus anginosus* are beta-hemolytic
  – *S. anginosus* react with Lancefield A, C, F or G antiserum
  – *S. mutans* has a Lancefield D reaction
VGS

• A motley crew of organisms that remain once you remove:
  – *S. pyogenes*
  – Lancefield group B organisms
  – Pneumococci
  – Enterococci
  – “Large colony” group C and G
Human Commensals

• Low pathogenic potential in immunocompetent hosts.

• Colonize:
  – Oral Cavity
  – Gastrointestinal Tract
  – Urogenital Tract
What’s Really in the Mouth?


- 206 pharyngeal and supragingival dental plaque samples
- Healthy children aged 4-18
Results

• VGS isolated from:
  – Pharyngeal swabs in 93% of children
  – Supragingival plaques in 72%

• 4-5 year olds
  – S. mitis

• 12-18 year olds
  – S. vestibularis

• S. mitis and anginosus recovered sporadically (2%)
Taxonomy of the VGS
Taxonomy

• 1906 Andrewes and Horder
• “Streptococcus mitis group”
  – S. mitis
  – S. salivarius
  – S. anginosus
Developing Taxonomy

• 1919 Orla-Jensen: *S. bovis*

• 1924 Clarke: *S. mutans*

• 1956 Guthof: “*Streptococcus milleri*”
  – Oral nonhemolytic streptococci
“Streptococcus milleri” group

- 1972 Coleman & Williams
  - Included minute beta-hemolytic and non-hemolytic oral streptococci

- 1987 Coykendall (International Journal of Systematic Bacteriology)
  - *Streptococcus anginosus* group
  - Approved name for these bacteria
  - Includes *S. anginosus*, *S. constellatus*, *S. intermedius*
Historical Nomenclature

• “Streptococcus milleri”
  – Not an approved bacterial name
  – Continues to be used in European and American literature
  – Continues to carry an important message to clinicians
  – Describes streptococci that cause suppurative infections
Basis of Old Taxonomy

• Phenotypic determinations
  – Biochemical characteristics
  – Amino acid hydrolysis
  – Sugar fermentation
  – DNA:DNA hybridization studies
Current Taxonomy

Sequence-based identification systems

• 16S rRNA gene sequencing
  – Poor resolution to species level of VGS
  – Some of these organisms have >99% gene sequence homology

• Alternate gene target sequencing
  – rnpB
  – Manganese-dependent superoxide dismutase gene
  – 16S-23S intergenic spacer region
  – D-alanine-D-alanine ligase gene
  – Hyaluronate lyase gene
• 16S rRNA
  – 16S ribosomal RNA
  – Component of the 30S subunit of prokaryotic ribosomes
  – 1542 nucleotides in length
  – Multiple sequences can exist within a single bacterium
Taxonomy

• Classification of VGS
  – S. mutans group
  – S. anginosus group
  – S. mitis group
  – S. sanguis group*
  – S. salivarius group
  – S. bovis group
Clinical Significance & Infections of the VGS
Clinical Significance

• VGS infections can result in significant morbidity and mortality

• Serious infections can occur when these organisms enter body sites that are usually sterile
Clinical Significance

- Infections can occur in health hosts

- Most commonly infections occur in:
  - Immunocompromised hosts
  - People with underlying cardiac abnormalities

- Pediatric infections
Clinical Significance

• VGS account for about one half of all cases of streptococcal endocarditis.

• *S. mutans* is responsible for dental caries.

• *S. anginosus* causes abscesses in the brain, liver and joints.
VGS Infections

- Endocarditis incidence
- Endocarditis in neutropenic patients
- Pediatric infections
- Abscesses and *S. anginosus*
- VGS in wounds
Infective Endocarditis

Endocarditis is an inflammation of the inside lining of the heart chambers and heart valves (endocardium).
Vegetation on Heart Valve

- The acute inflammation caused by the infection resulted in the formation of a "vegetation" on the valve, comprised of a mixture of thrombus ("blood clot"), bacteria and inflammatory cells.
Infective Endocarditis (IE)

- Gram positive bacteria are the most frequently identified causes:
  - Adhere to heart valves
  - >80% of all IE cases are caused by *Staphylococcus aureus*, *Streptococcus* spp, and *Enterococcus* spp.
Endocarditis

• *Streptococcus bovis*
  – Patients aged >60 years
  – Causative organism in 10% of cases of IE
  – Accompanied by abnormalities of the digestive tract, particularly colon carcinoma and villous adenoma.

Bacteremia and IE in Immunocompetent Adults & Children

• Clinical signs and symptoms
  – Upper respiratory tract symptoms
  – Lower respiratory tract symptoms
  – Post-seizure
  – Temperature >37°C
  – Hypotension

Bacteremia and IE in Immunocompetent Adults & Children

- **VGS cause of community acquired bacteremia**
  - 6.9% (50/723) adult patients
  - 12.3% (13/106) pediatric patients

- **Endocarditis**
  - 11.6% of adults
  - No children

- **30 day mortality**
  - 7.3%

IE in Neutropenic Patients

• IE caused by VGS in this high risk population:
  – 39% of bacteremia cases are due to VGS
  – VGS are the most frequent cause of IE

• The most frequently isolated species in blood culture are:
  – *Streptococcus mitis*
  – *Streptococcus sanguis II*

IE in Neutropenic Patients

- Mortality rates range from 6% to 30%.

- Case-control studies have identified the following risk factors:
  - severe neutropenia (< 100 neutrophils/mm³)
  - prophylactic antibiotic treatments with quinolone or co-trimoxazole
  - absence of intravenous antibiotics at the time of bacteremia
  - high doses of cytosine arabinoside
  - oropharyngeal mucositis
  - heavy colonization by viridans streptococci

Pediatric IE Infections

• IE occurs less frequently than in adults (1 per 1000 admissions):
  – Pediatrics: 1 per 1280 pediatric admissions

• VGS is the most common cause if IE in children
  – 20-43%

• Mortality rate is low (5.3%)

Pediatric IE Infections

• VGS symptoms
  – Prolonged low grade fevers
  – Arthralgias
  – Myalgias
  – Weight loss
  – Rigors
  – Fatigue
  – Weakness

• Very common for children to have continuous bacteremia

Pediatric CF Infections

• *S. anginosus* may be a significant pathogen
  – Associated with colonization with *Pseudomonas aeruginosa*.
  – Patients responded clinically and microbiologically to *S. anginosus* directed therapy (that had no activity to *P. aeruginosa*)
Pediatric Cancer Patients

- IE with VGS is common
  - Infections predominantly with *S. mitis* and *S. oralis*.

- Mucositis is an important risk factor as it provides a route of entry for VGS.
Infections by the Anginosus Group

• Suppurative infections (abscess formation):
  – Bacteremia
  – Endocarditis (3-15% of VGS)
  – Brain abscess
  – Pleural empyema
  – Lung abscess
  – Maxillary sinusitis
  – Intra-abdominal abscess
  – Infection of pacemaker
  – Infection of vascular graft
  – Skin and soft tissue
Infections by the Anginosus Group

- Often isolated with other organisms (such as anaerobes)
  - Japanese study of 68 hospitalized patients with S. anginosus group infections
    - 18% of cases were pure cultures
    - 82% cases were mixed cultures

Infections by the Anginosus Group

• Sites of clinical infection:
  – *S. anginosus* most frequently identified in the gastrointestinal tract and genitourinary specimens
  – *S. constellatus* most frequently identified from the respiratory tract
  – *S. intermedius* showed an association with infections of the central nervous system.

VGS Brain Abscess

- Viridans streptococci from dental procedures can seed to the heart.

- Literature reports of cases of VGS brain abscesses following dental procedures and maxillofacial trauma.
VGS Brain Abscess

• A 19-year-old male patient.
  – Diagnosed with *S. sanguinis* brain abscess
  – Unknown etiopathology
  – Subclinical endocarditis

• Highlights the importance of:
  – Prompt diagnosis
  – Initiation of antimicrobial therapy
  – Given the potential for long-term sequelae such as focal deficits and seizures

S. anginosus Group
Wound infections

• Intravenous drug users:
  – Septic complications occur frequently at the injection site
  – In the groin large abscesses around the femoral vessels can threaten life or limb.
  – Antecubital abscesses and bacteremia
Abscess Formation

- Marked swelling and redness is apparent just above antecubital fossa.

- This is caused by an abscess, the result of bacteria inoculated under the skin during injection drug abuse.
Antimicrobial Susceptibilities of the VGS
General AST Principles

• Often, knowledge of the taxonomic identity of bacteria causing the clinical infection can be used to predict the antimicrobial susceptibility patterns of the organism.

• But the VGS have undergone many rearrangements in taxonomy!
VGS Generalizations

• Antimicrobial resistance is substantial in the VGS as a group
• Penicillin resistance is high
  – 48% in USA strains
  – 45% in Canadian strains
  – 33% in Latin American strains.

Penicillin Resistance

• *S. mitis:*
  – Was the most common species identified in clinical samples
  – Was the species most likely to be penicillin resistant

• *S. oralis:*
  – Found to be (with *S. mitis*) most common in blood cultures of cancer patients
  – Commonly resistant to beta-lactam antibiotics

Penicillin Resistance

• *S. sanguis* group:
  – Resistance is also present but not as high as in the *S. mitis* group organisms.
S. mitis Group

• Among the VGS this group is most likely to become resistant to beta-lactams and macrolides.

  – Penicillin 16-34% R
  – Clindamycin 4-14% R
  – Erythromycin 40-51% R
  – Tetracycline 29-34 resistance R

**S. mitis Group Resistance**

- Implications of the emergence of resistance in VGS group are serious:
  - *S. mitis/oralis* are closely associated to *S. pneumoniae*
  - Similar species can transfer genetic material
  - Development of pneumococcal resistance to penicillin
S. anginosus Group

- **Penicillin:**
  - Resistance to beta-lactams is emerging

- **Macrolides:**
  - Resistance was found in 17% of strains

S. anginosus Group

• Species of *S. anginosus* group were identified by 16S rRNA (*S. anginosus, S. constellatus, S. intermedius*)
  – There was no difference found in the susceptibility patterns for the three species
  – Identification to the “milleri/anginosus group” may be sufficient for patient management and it’s not necessary to go to species level.

Antibiotic Usage

• Antibiotic usage drives resistance of penicillin and macrolides in VGS

• In pediatric and adult populations the most at risk for developing resistant and invasive VGS infections are the immunocompromised
  – This is also a population that receives frequent antibiotic treatment.
Antibiotic Usage

• Study by Kastner et al 2001 found that macrolide resistance developed in VGS in children treated for URTI
  – Initial pretreatment cultures taken
  – Antibiotics: azithromycin or clarithromycin
  – 1 week post-treatment 60% of patients had at least one macrolide-resistant organism
  – 6 weeks later 87% of patients treated with azithromycin were colonized with macrolide-resistant VGS (60% in clarithromycin group)

“The Good News”

• VGS remain susceptible to a group of antibiotics:
  – Vancomycin
  – Linezolid
  – Daptomycin
Emerging Problem

• VGS have developed resistance to penicillin and macrolide (MLS) antibiotics
• There are some group-specific resistance patterns
• Resistance to antibiotics is increasing the virulence of *S. pneumoniae* (a well defined human pathogen)
The Role of the Clinical Laboratory
Sterile Body Fluids

• Culture examination
  – Examine all inoculated plates and broth for growth at 24 hours
  – Reincubate if there is no visible growth
  – Read the plates daily for 4 additional days for invasively collected specimens

• Blood cultures
  – Incubate for 5 to 7 days

Sterile Body Fluids

• Cultures with growth on media
  – Notify your microbiologist
  – Correlate the culture results with those of the Gram stain made from the specimen
  – Identify all organisms

• The clinical picture can help direct us.
AST and Sterile Body Fluids

• Most viridans strep tested for AST are from serious infections
  – Report MIC
  – Report S/I/R

• MIC is clinically used to treat VGS bacteremia/endocarditis
Non-sterile Sites

• Aerobic Bacteriology Section
  – Chapter 3.13 “Wound Cultures”
    • Wound Abscesses and Soft Tissue Cultures
• Table 3.13.1-1 Aerobic and Anaerobic Isolates from Acute and Chronic Infections
  – Lists Streptococcus spp. (viridans group)
• Figure 3.13.1-5 Initial evaluation of positive wound cultures for organisms growing aerobically
  – A picture is worth a thousand words!!

Non-Sterile Sites

• Note: There are microorganisms that are usually considered significant even if isolated in low numbers or with mixed flora
  – Group A Streptococci
  – Group B Streptococci
  – Pseudomonas aeruginosa
  – etc
Non-Sterile Sites

• Generally identify VGS if isolated with 2 other organisms in a mixed culture (3 microorganisms) IF
  – WBCs seen on direct smear
  – The specimen was collected from a normally sterile site
  – The specimen is of good quality (few epithelial cells)
  – The organism was seen on the direct smear
Non-Sterile Sites

• Minimal testing for non-invasively collected specimens IF:
  – Many epithelial cells seen in direct smear
  – No inflammatory cells seen in direct smear and no clinical information available to indicate an infection
  – >3 organisms growing
Non-Sterile Sites

• Identify VGS to the genus level
  – Surgically collected specimens (biopsy)
  – Invasively collected specimens
  – If single or predominant pathogen
  – Inflammatory cells seen on the gram stain
Non-Sterile Sites

• May not need to identify VGS to the genus level if:
  – Very mixed culture
  – Not predominant
General Principles

• A positive culture indicates infection with the organism.
• WBCs are usually present in infections of body fluids.
• FP cultures can result from contamination of the specimen with flora.
• FN can be caused by low numbers of organisms, prior antibiotics or the fastidious nature of the infective organism.

Overview

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Summary of the VGS

- **S. mutans group**
  - S. mutans, S. sobrinus
- **S. anginosus group**
  - S. anginosus, S. constellatus, S. intermedius
- **S. mitis group**
  - S. mitis, parasanguis, gordonii, cristatus, oralis, infantus, peroris, pneumonieae
- **S. sanguis group***
- **S. salivarius**
  - S. salivarius, S. vestibularis, S. thermophilus
- **S. bovis group**
  - I S. equinus (used to be S. bovis)
  - II S. gallolyticus
  - III S. infantarius
  - IV S. alactolyticus
Thank you.

Happy Holidays!