Use of antibiotics in Infection-Associated Neuropsychiatric Syndromes including PANS

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Conflicts of interest

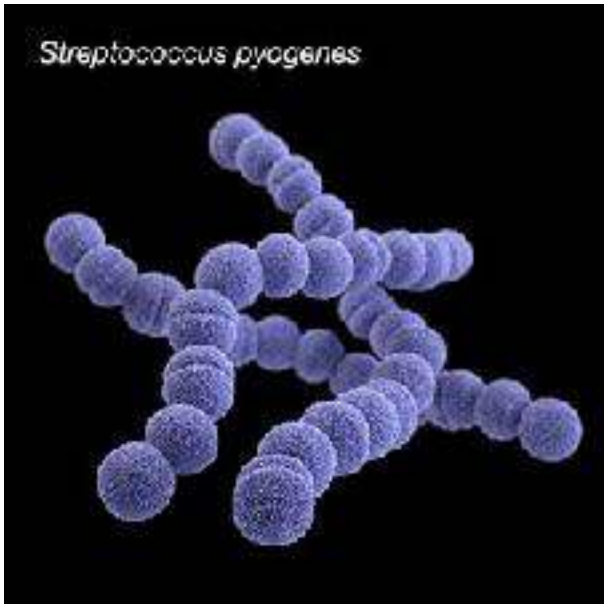
- Equity – Merck Corporation

Why are we interested in infections in general and GAS infections in particular?

- Incidence of childhood –onset obsessive compulsive disorder is associated with increased lifetime incidence of selected infections and autoimmune disorders:
- Scarlet fever (4.0% vs. 1-2% estimated population incidence)
- Encephalitis or meningitis (1.4 vs. 0.1-0.4%)
- Rheumatic fever (0.6% vs. 0.1-0.2%)
- Rheumatoid arthritis (1.1% vs 0.2-0.4%)
- Asthma (17.2% vs. 11.9-14.3%)
- No differences with SLE, diabetes mellitus, psoriasis, ulcerative colitis, Crohn's disease
- Similar increased incidence observed with first degree relatives, regardless of any OCD symptomatology
- This is consistent with an infectious/inflammatory trigger for OCD symptoms [Westwell-Roper C et al, J Child Adolesc Pschopharmacol 2019]

A Primer on Streptococci

- Streptococci are members of a large genus of gram-positive oval or round bacteria that are found in pairs and chains.
- Streptococci are distinguished from staphylococci by lacking the enzyme catalase and by their growth in chains rather than in clusters.



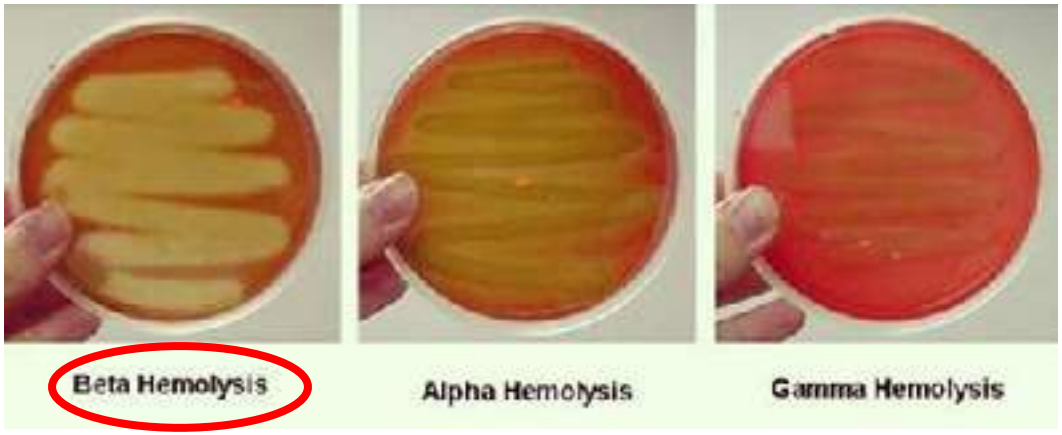
A Primer on Streptococci

Classification of streptococci by hemolytic properties on blood agar:

Alpha hemolysis: partial red cell lysis, with reduction of hemoglobin→green pigmentation [hydrogen peroxide production]

Beta hemolysis: lysis of red blood cells→clear halo around colonies [hemolysins S, O]

Gamma hemolysis: no changes seen on blood agar



Classification of β hemolytic streptococci

Rebecca Lancefield
1895 - 1981

developed a classification of β hemolytic streptococci based on antibody reactions against surface carbohydrates:
There are 20 distinct groups (A–U [no I, J])
Most Lancefield groups contain 1 species [e.g. GAS=S.

Lancefield Groups: GAS is the dominant upper respiratory pathogen

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TABLE 1. *Comparison of Carrier Rates of Various Lancefield Groups of Beta-Hemolytic Streptococci in 3853 Normal Soldiers and 3026 Hospitalized Soldiers with Respiratory Infections.*

Organism	Rates in Normal Soldiers				Rates in Hospitalized Soldiers*
	March-May, 1944	January, 1945	March, 1945	1944-1945 combined	1943–1945
	%	%	%	%	%
Group A	5.2	4.6	6.7	5.4	9.5
Group B	—	0.2	0.3	0.1	0.2
Group C	1.0	1.9	1.5	1.4	1.8
Group F	0.1	0.2	0.2	0.2	0.1
Group G	1.6	2.3	0.7	1.6	1.4
Group L	—	—	—	—	0.1
Combination	—	—	—	—	0.1
Not grouped	0.1	0.2	0.3	0.2	0.7
Total carrier rate	8.0	9.4	9.7	8.9	13.9
Number of cultures taken	1585	1229	1039	3853	3026

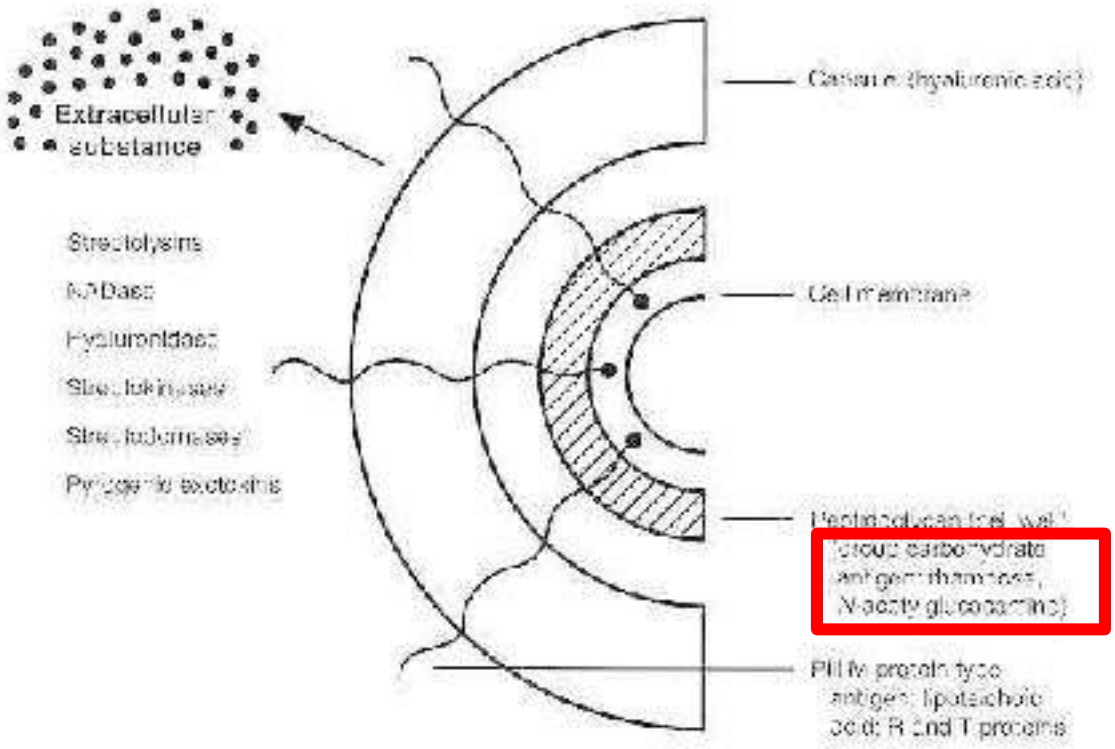
*Admission cultures.

TABLE 3. *Lancefield Groups of Beta-Hemolytic Streptococci Isolated from Throat Cultures of 161 Patients with Respiratory Disease Who Developed Specific Antibodies During Convalescence.*

Organism	Total No. of Patients	Percentage of Total
Group A	139	86
Group A with other groups	7	4
Group C	7	4
Group G	5	3
Not grouped and others	3	2

Commission on Acute Respiratory Diseases. New Engl J Med 1947;236:1157.

Group A streptococci - structure

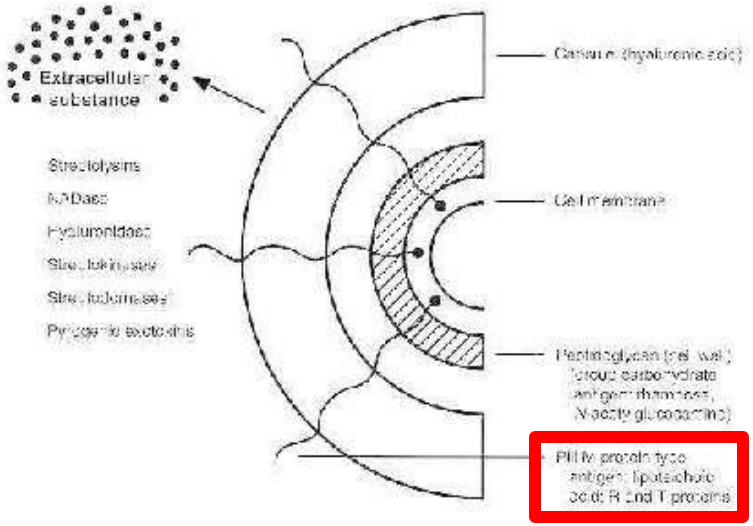


Baron S ed. Medical Microbiology, 4th ed. 1996

Group A streptococci Diversity

- There is **great diversity** among GAS isolates
- **M protein** = surface pilus. Serves as a virulence factor and inhibits complement deposition and phagocytosis
- There are ~150 distinct M proteins identified by protein characterization
- There are **~230 distinct M proteins identified by *emm* gene sequencing**
- **T factor = another surface protein**

  with at least 25 distinct types



Group A streptococcal epidemiology is complex – there are MANY GAS strains

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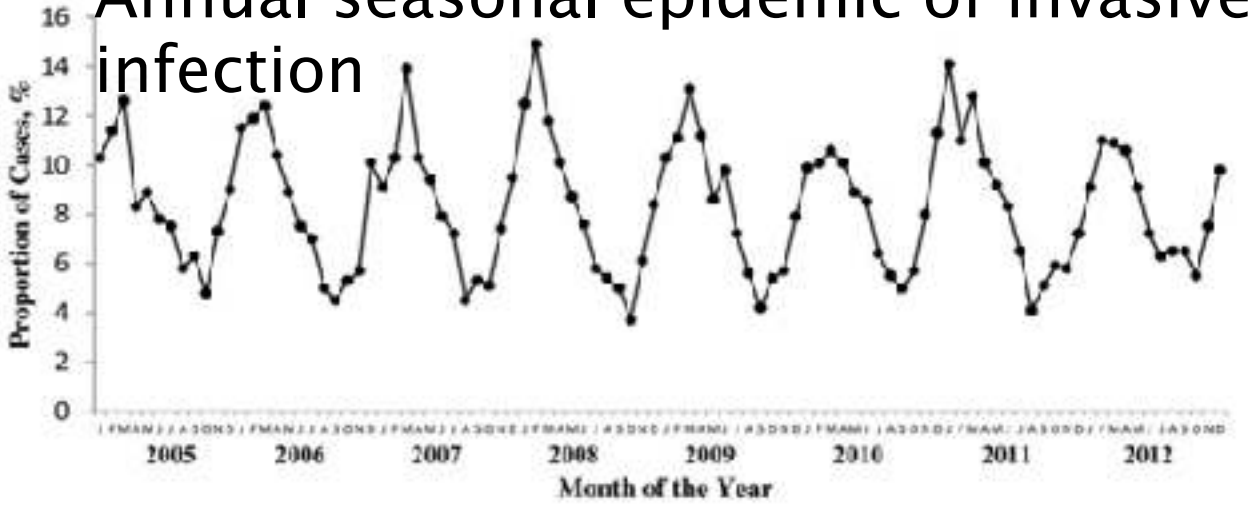
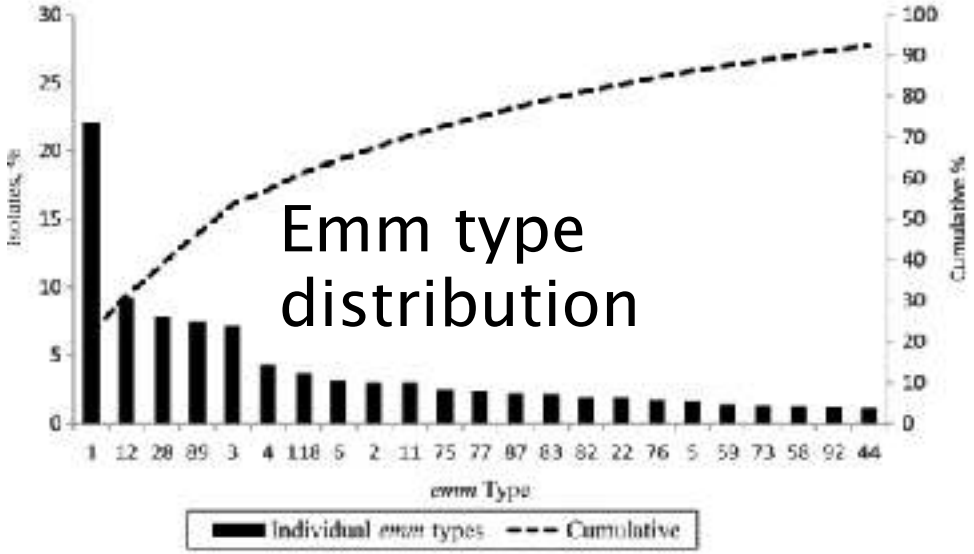
Annual seasonal epidemic of invasive GAS infection

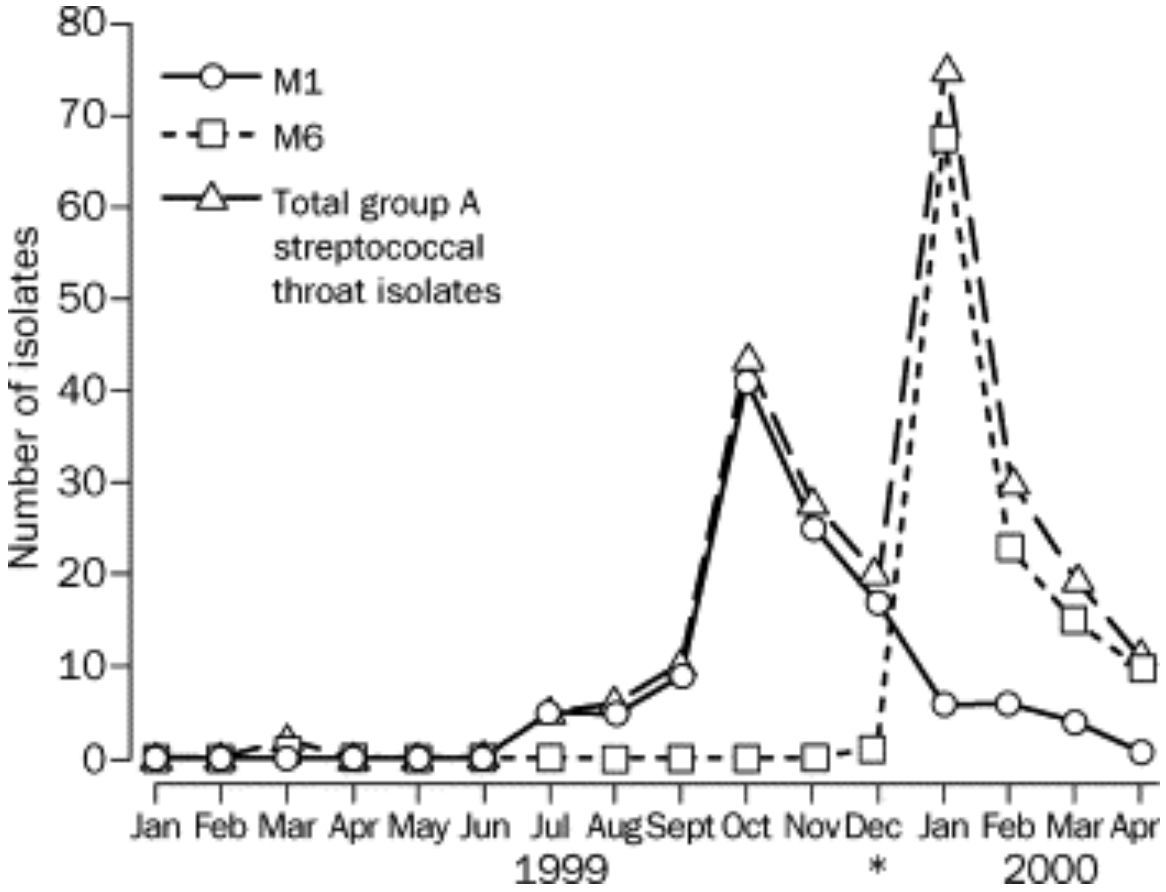


Emm type distribution



Nelson GE et al. Clin Infect Dis 2016;63:478

A single M type dominates each season



Kaplan EW et al. Lancet 2001; 358:1334

M serotypes of Group A streptococci and nonsuppurative (immunologic) sequelae

Acute Rheumatic Fever	Pharyngitis associated GN	Pyoderma associated GN
1	1	2
3	4	49
4	12	55
5	25	57
14		59
18		60
19		61
24		

Shulman S et al. Principles and Practice of Infectious Disease, 9th edition. Bennett JE, Dolin R, Blaser M eds, 2019

GAS pathogenesis

- GAS are strictly human pathogens
- Person-to-person spread is largely through droplet spread and salivary contact
- GAS have adhesive, anti-complement and anti-phagocytic surface structures to promote adhesion to epithelia

1. GAS elaborate multiple extracellular products:

➢ Streptolysins (O,S) lyse red cells, white cells, and platelets

➢ Multiple enzymes (including anti-DNase B) liquefy pus to promote spread of infection though host tissues.

➢ Streptococcal exotoxins = **superantigens** associated with toxic shock syndrome, necrotizing fasciitis, and other life-threatening infections. Superantigens active large numbers of T cells leading to “cytokine storm”.

GAS can cause focal infection throughout the body!

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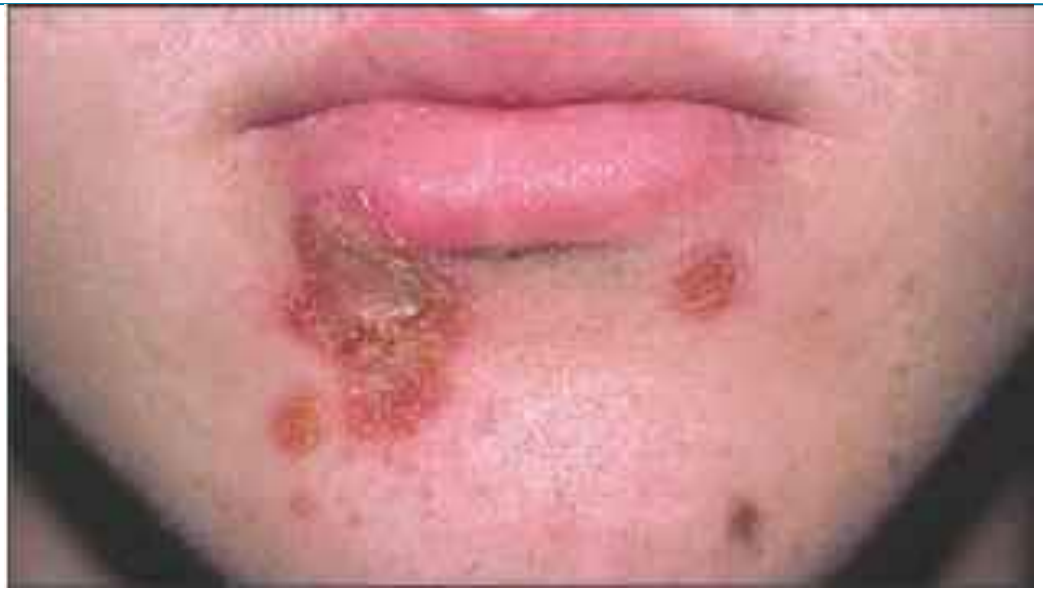
Skin infections:

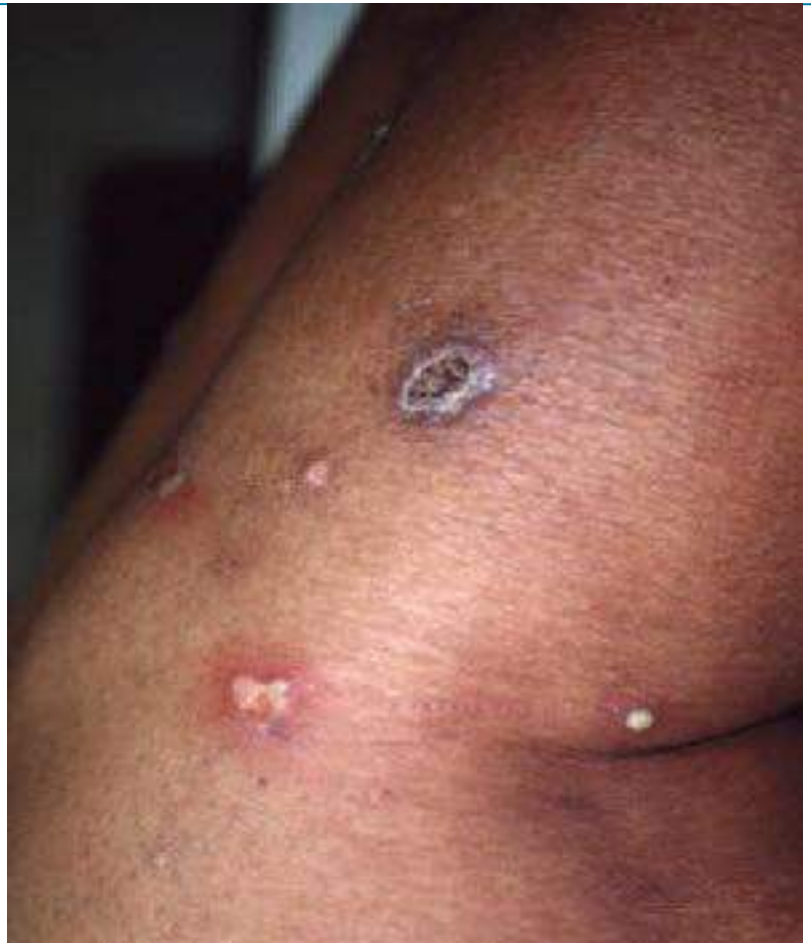
- Impetigo
- Perianal dermatitis
- Ecthyma
- Erysipelas
- Cellulitis
- Lymphangitis
- Streptococcal gangrene
- Necrotizing fasciitis
- Purpura fulminans

Impetigo



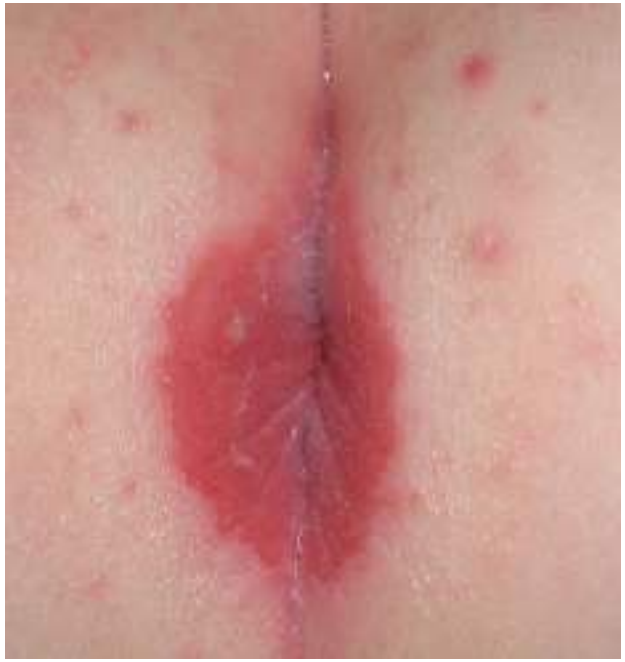
Superficial skin infection caused by GAS +/- S. aureus
Usually develops at sites of superficial skin injury: (eczema, insect bites, abrasions)
Associated with “honey-colored” crusting
Superficial skin infections selectively associated with kidney complications

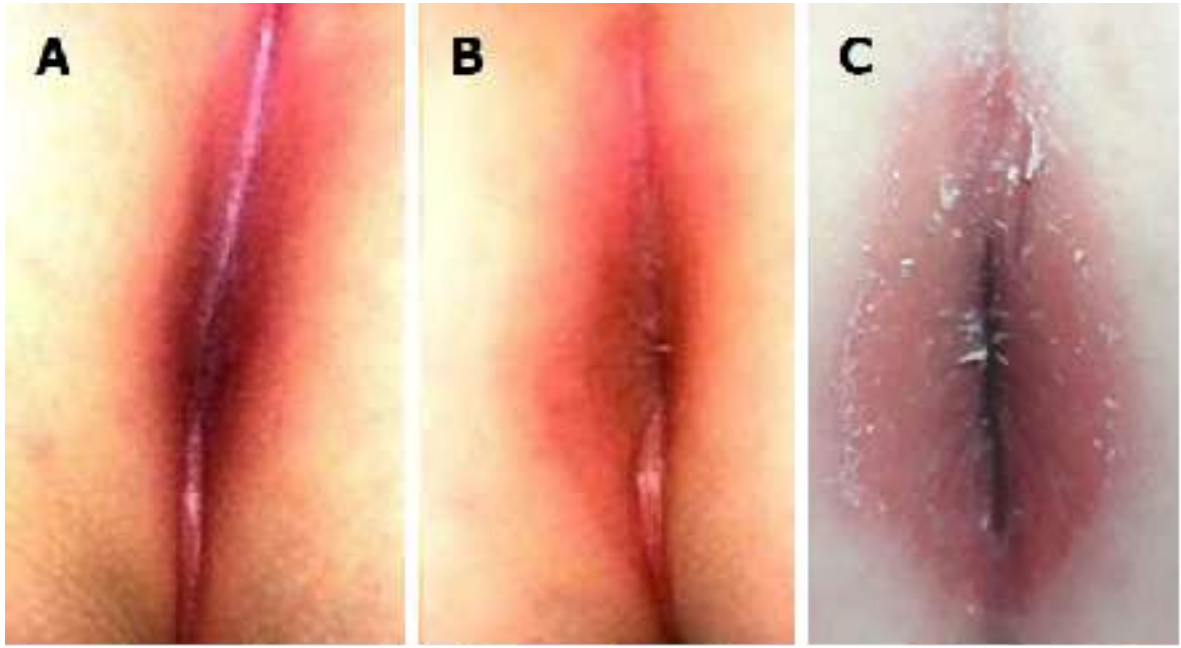
ecthyma



Superficial lesions which penetrate the dermis:
Pustule→crusting ulcer→scarring

Perianal streptococcal dermatitis



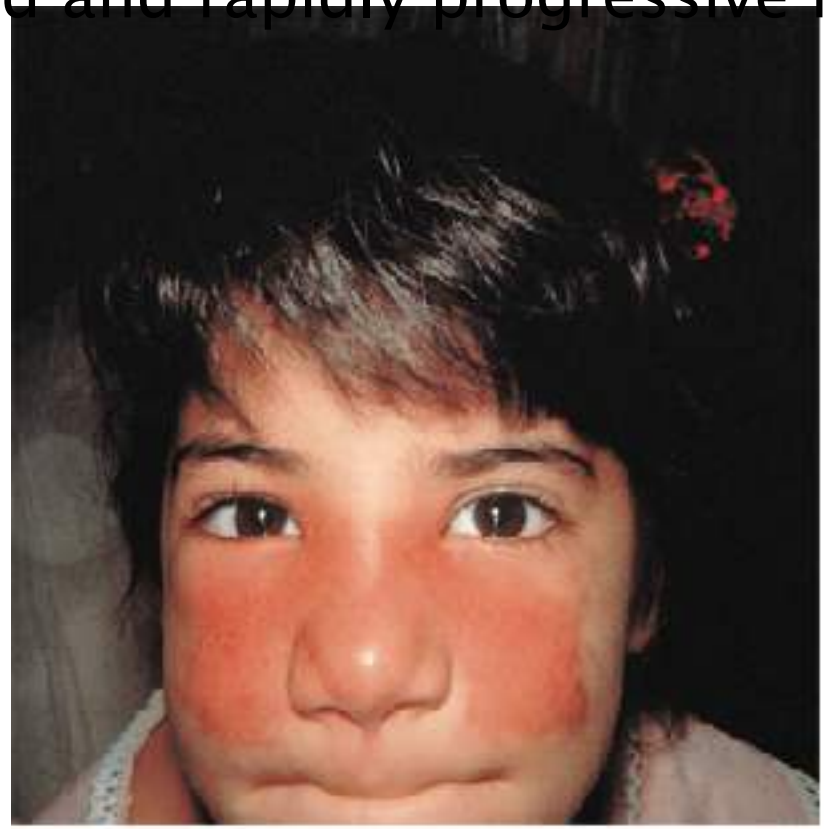


Serban ED. World J Pediatr 2018;7:89

erysipelas

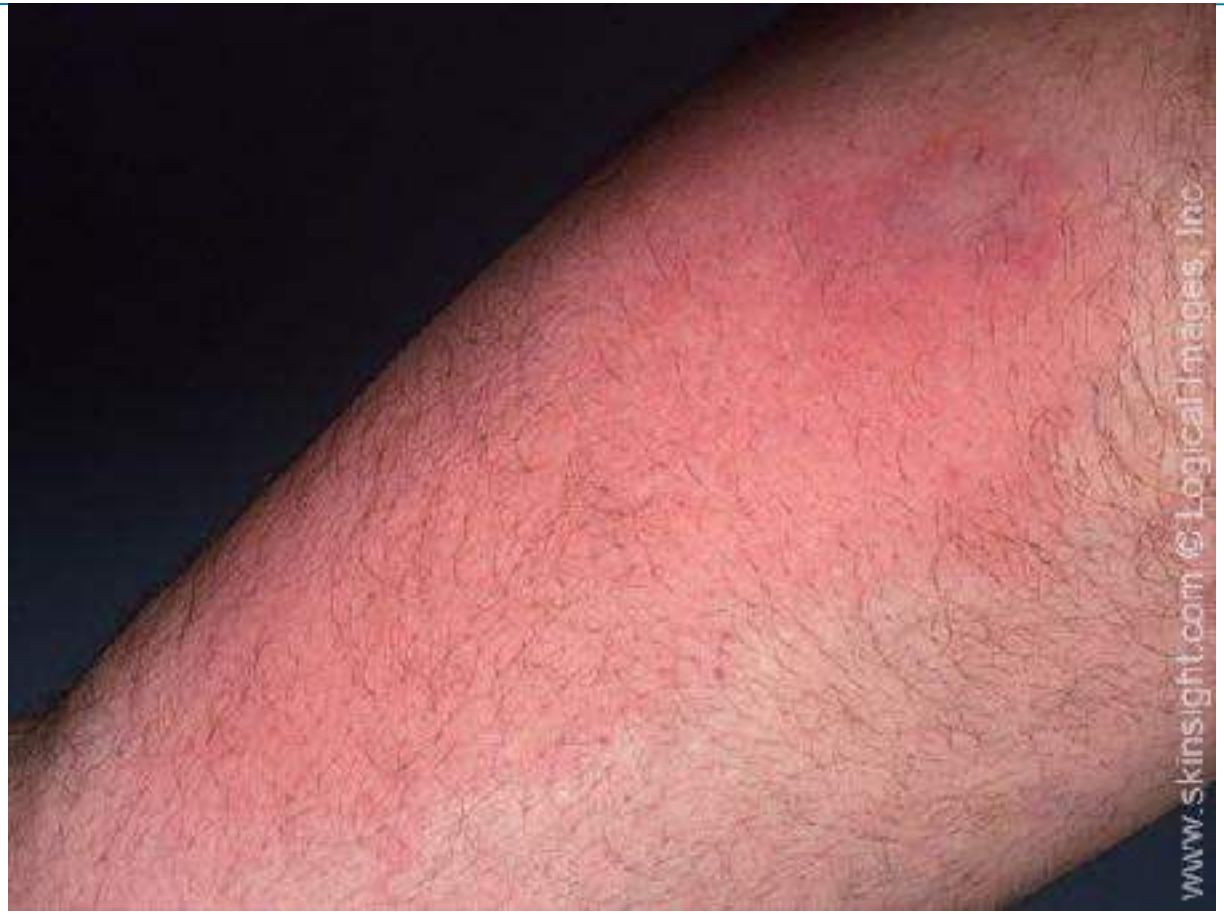
Superficial cellulitis with prominent lymphatic involvement

Painful raised and rapidly progressive rash with sharp borders



Source: J.E. Tintinalli, J.S. Stapczynski, O.J. Ma, D.M. Yealy, G.D. Meckler, D.M. Cline: Tintinalli's Emergency Medicine: A Comprehensive Study Guide, 8th Edition
www.accessmedicine.com

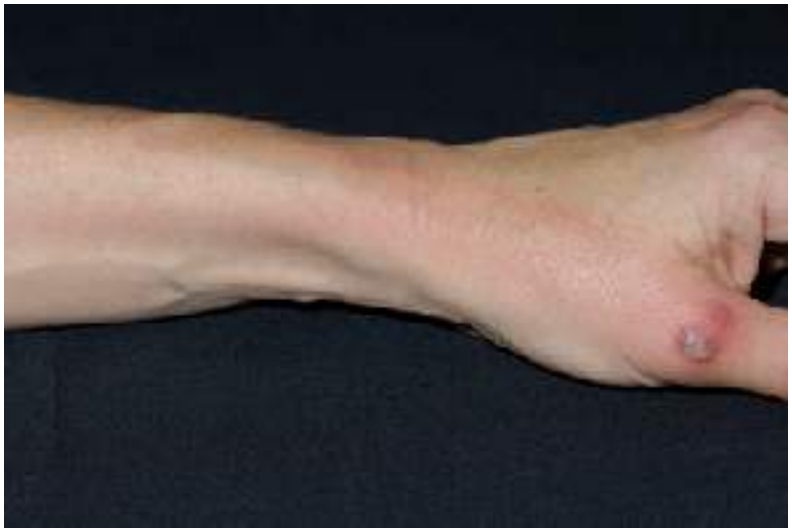
cellulitis



Deeper skin infection, involves subcutaneous tissues
Borders less well demarcated

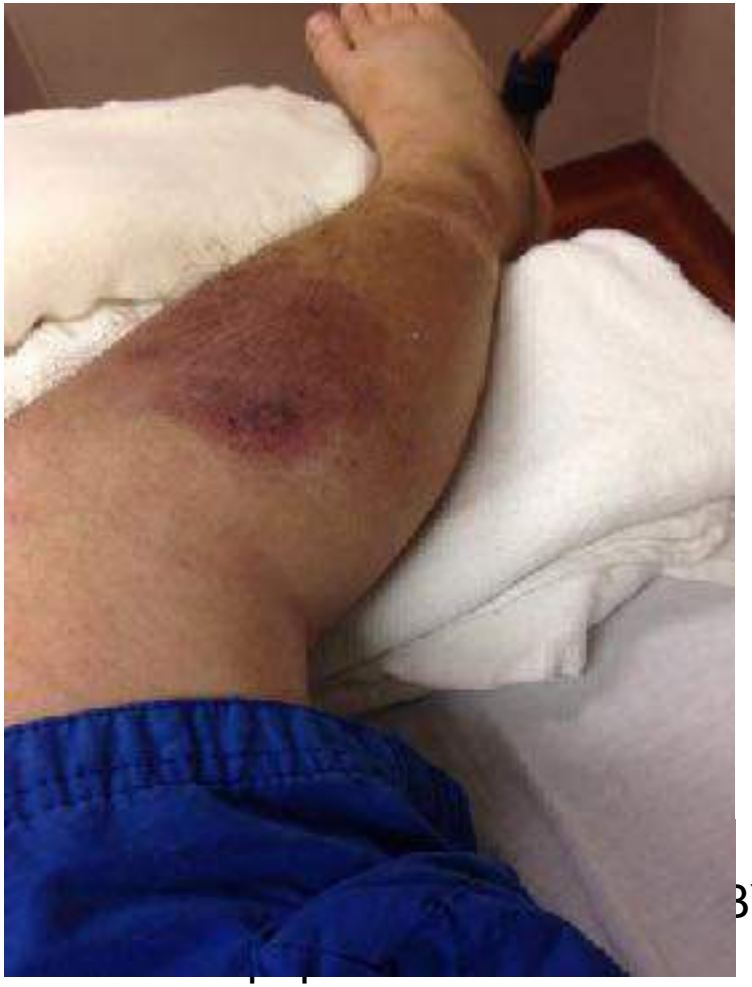
lymphangitis

Rapidly progressive infection with initial cutaneous focus but spread of infection through the lymphatic channels, with characteristic linear streaking



https://www.gponline.com/bacterial-infections/article/1059441

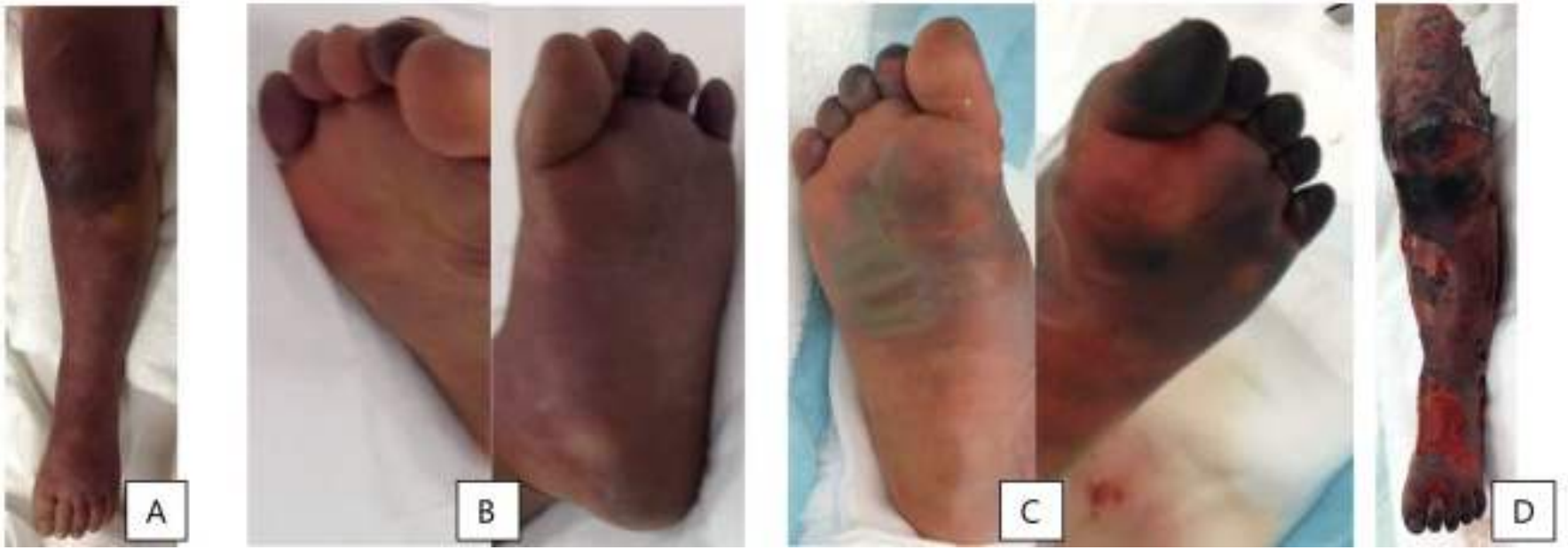
Skin infections requiring urgent surgery:
Streptococcal gangrene
Necrotizing fasciitis/streptococcal myositis



BY-SA 4.0, https://commons.wikimedia.org/w/

Streptococcal purpura fulminans

Syndrome of vascular thrombosis with widespread tissue loss-seen with GAS but more commonly with N. meningiditis



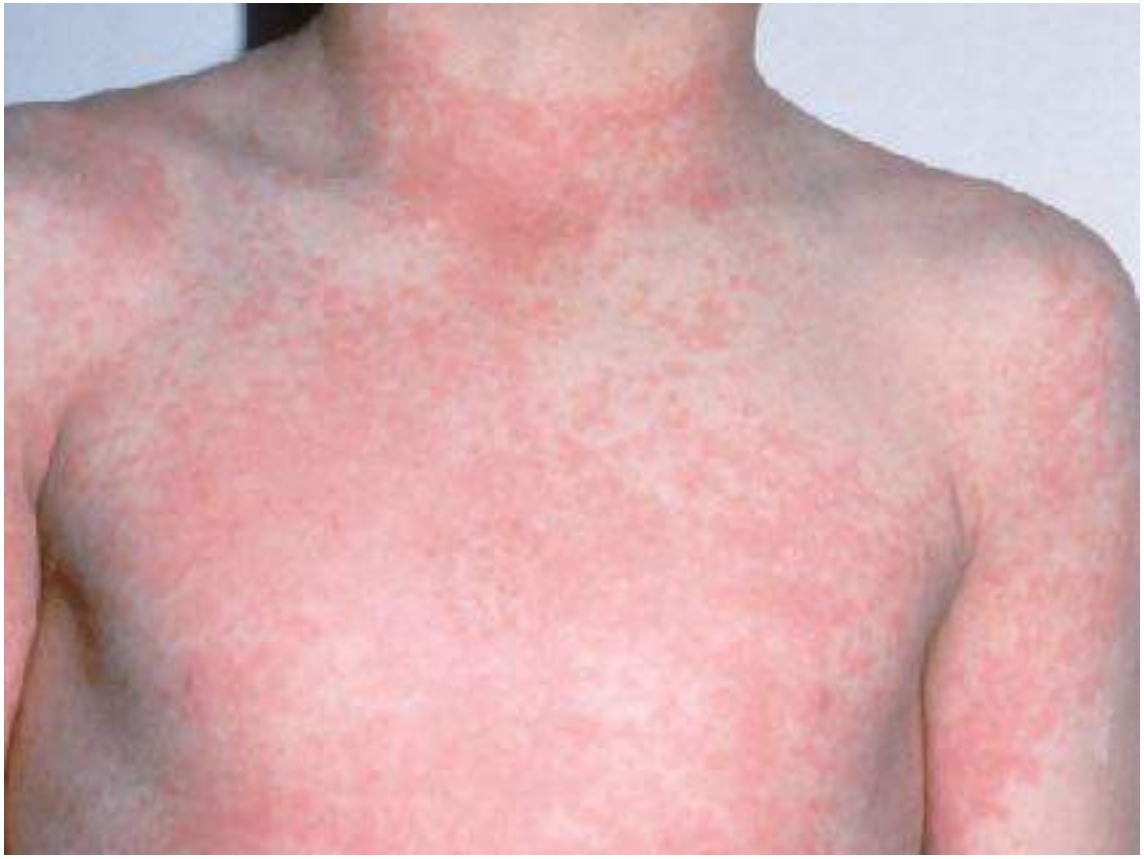
Okuzono S et al. Ann Clin Microbiol Antimicrobial 2018;7:31.

Nonsuppurative skin disorders

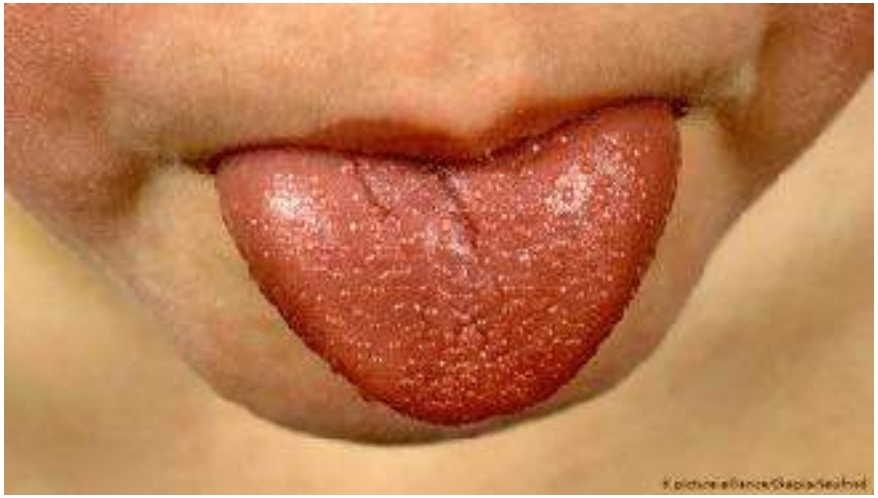
- Scarlet fever
- Toxic shock syndrome
- Guttate psoriasis
- Erythema marginatum

Nonsuppurative skin disorders
Scarlet fever = strep throat with a rash!

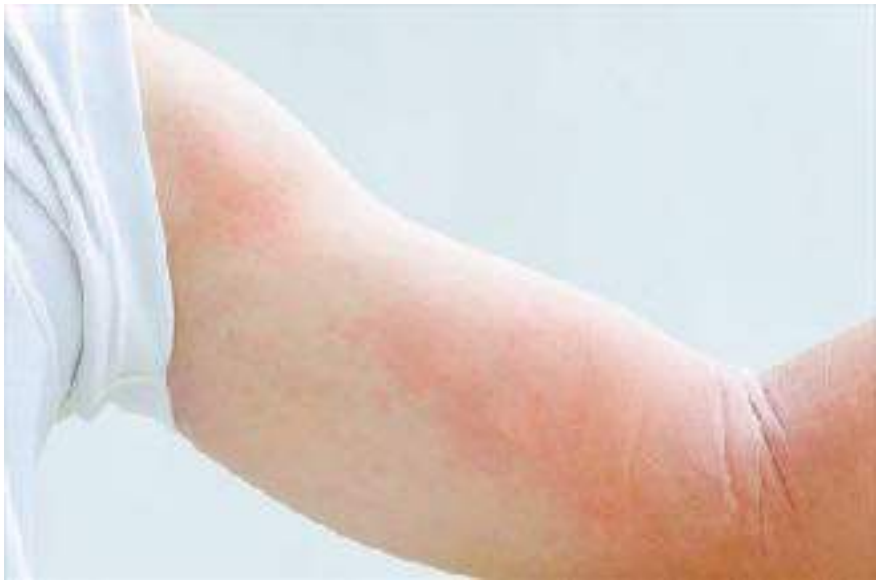
- diffuse erythematous rash due to the production of pyrogenic exotoxin, most commonly associated with pharyngitis



Nonsuppurative skin disorders
Scarlet fever

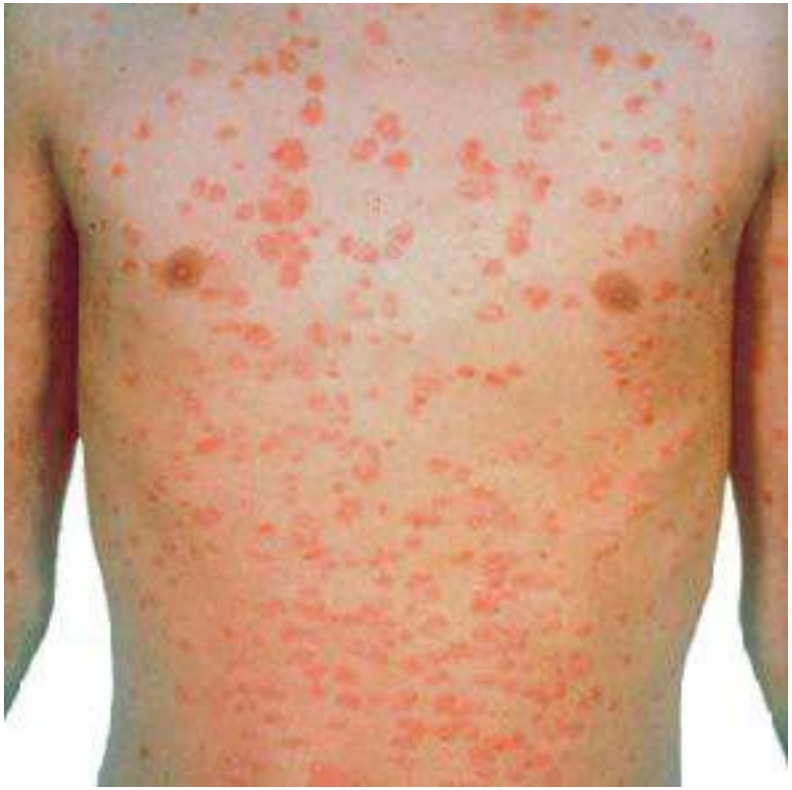


Strawberry tongue



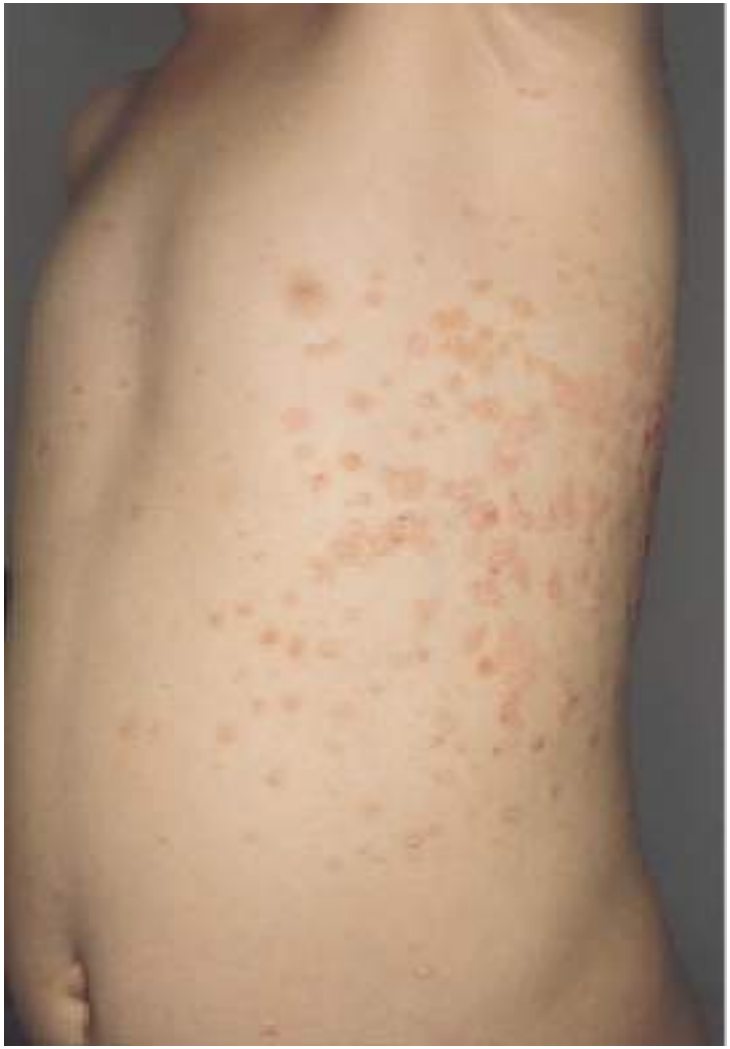
Pastia's lines

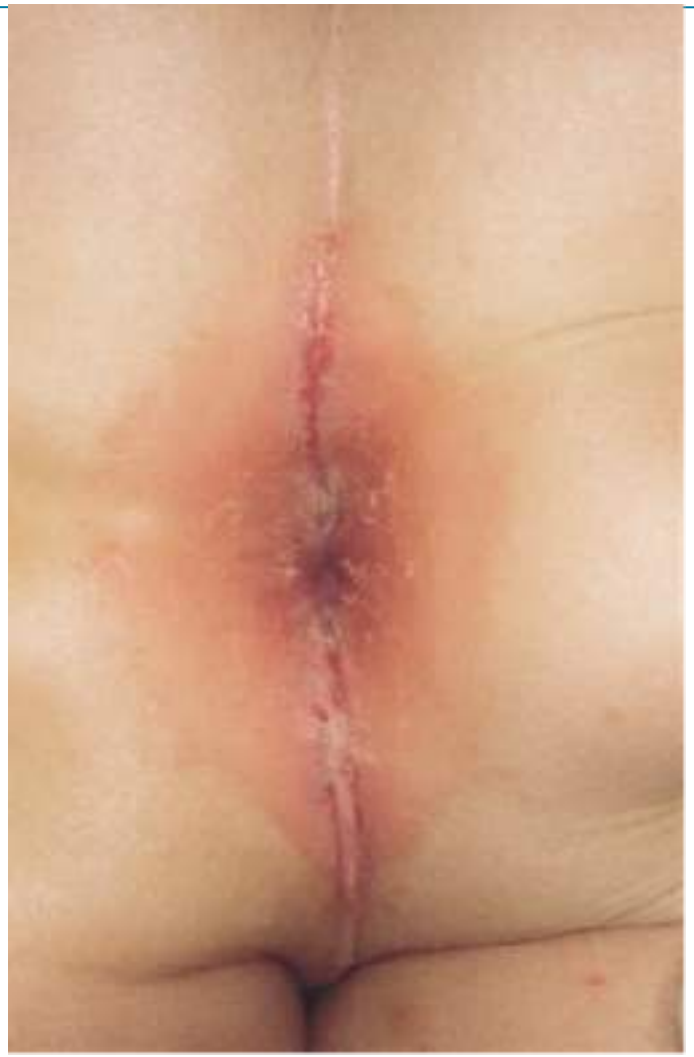
Nonsuppurative skin disorders guttate psoriasis



Uncommon; may follow GAS infection by 2-3 weeks

Guttate psoriasis triggered by perianal streptococcal dermatitis

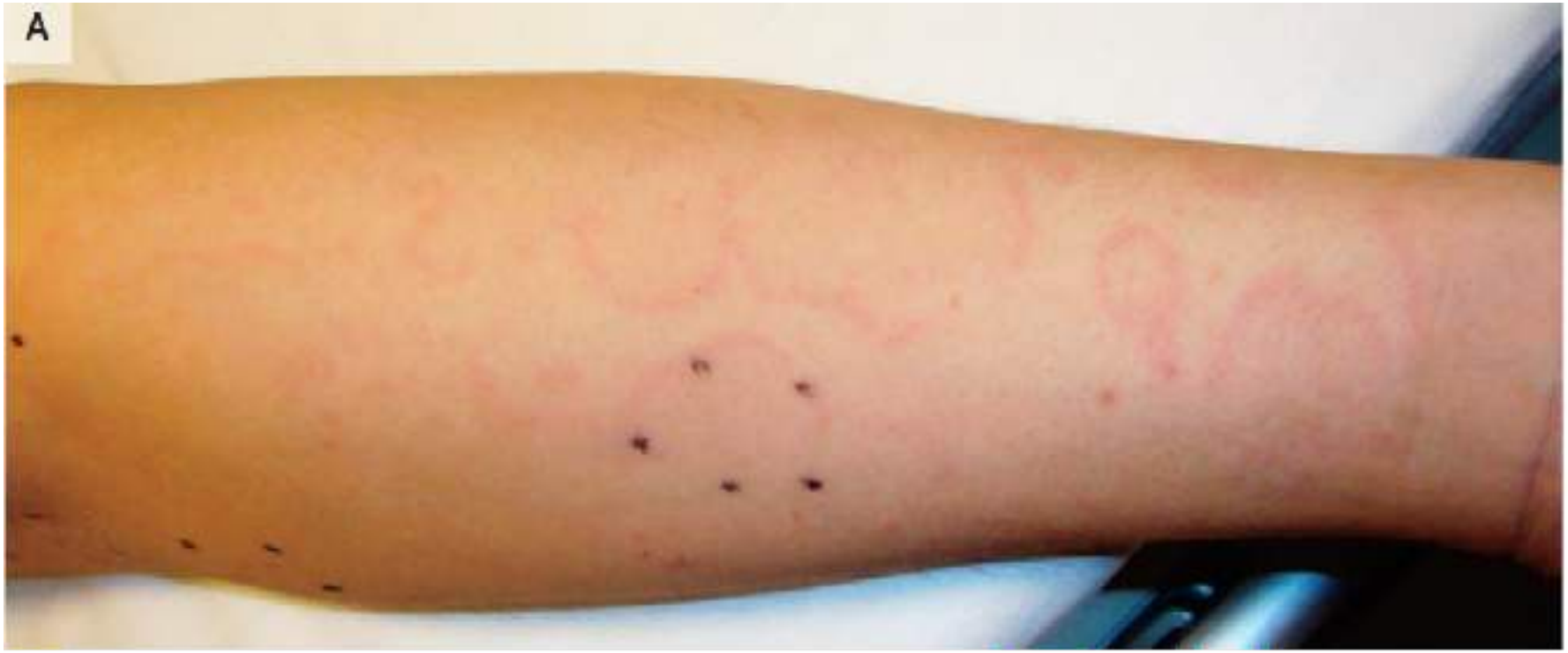




Herbst RA et al. J Am Acad Derm 2000;42:885

Erythema marginatum

A major criterion for acute rheumatic fever



Saito M et al. New Engl J Med 2016;375: 25.

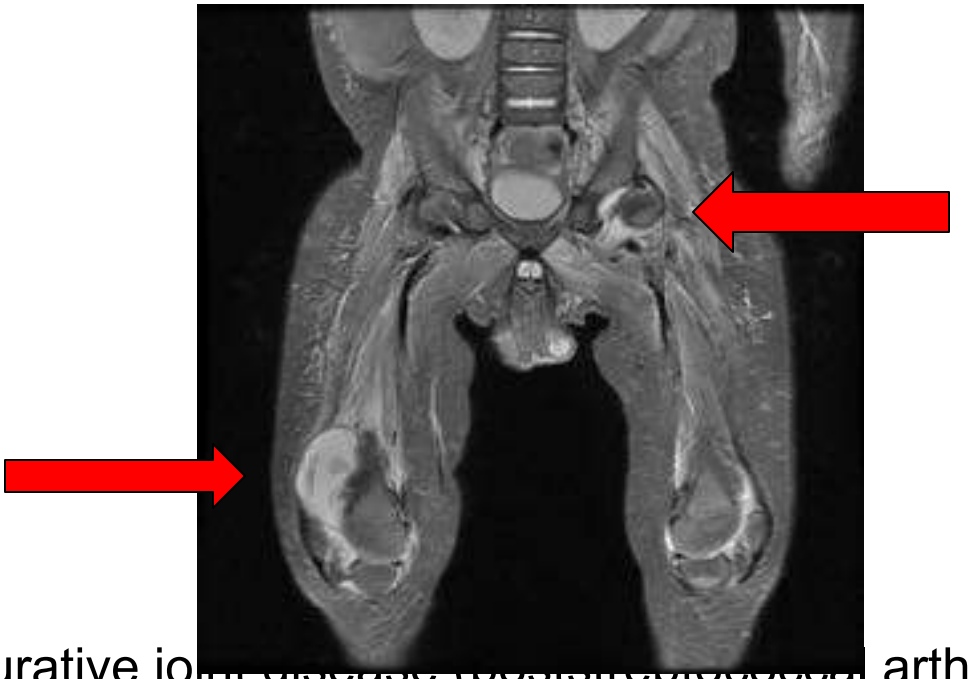
Central nervous system infection

- Meningitis (often complicating primary sinusitis, otitis, or mastoiditis)
- Spinal epidural abscess
- Bacteremia may complicate ENT focus or primary cutaneous focus with seeding of the cerebrospinal fluid

Quach V et al. Pediatrics 2002; 109 (1)

Skeletal infection

- Osteomyelitis
- Septic arthritis
- Skeletal complications are the result of bacteremia with seeding of the bones or joints. Multiple concurrent sites of infection are not unusual.

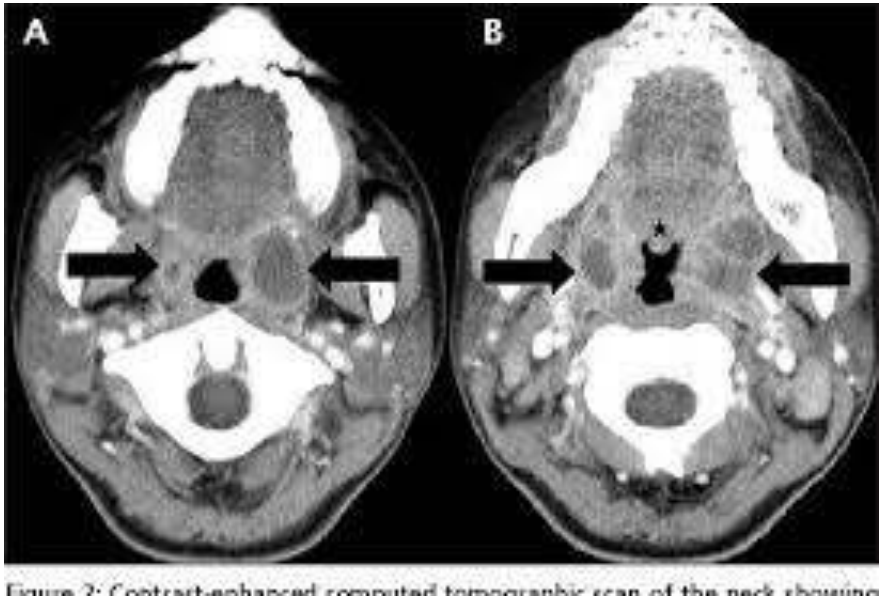


- Nonsuppurative joint disease (poststreptococcal arthritis, ARF)

ENT/Respiratory tract infections

- Pharyngitis/tonsillitis
- Peritonsillar abscess and its complications:
  deep neck soft tissue infections—lateral and posterior pharyngeal abscesses
- Otitis media
- Sinusitis
- Adenitis
- Pneumonia/empyema

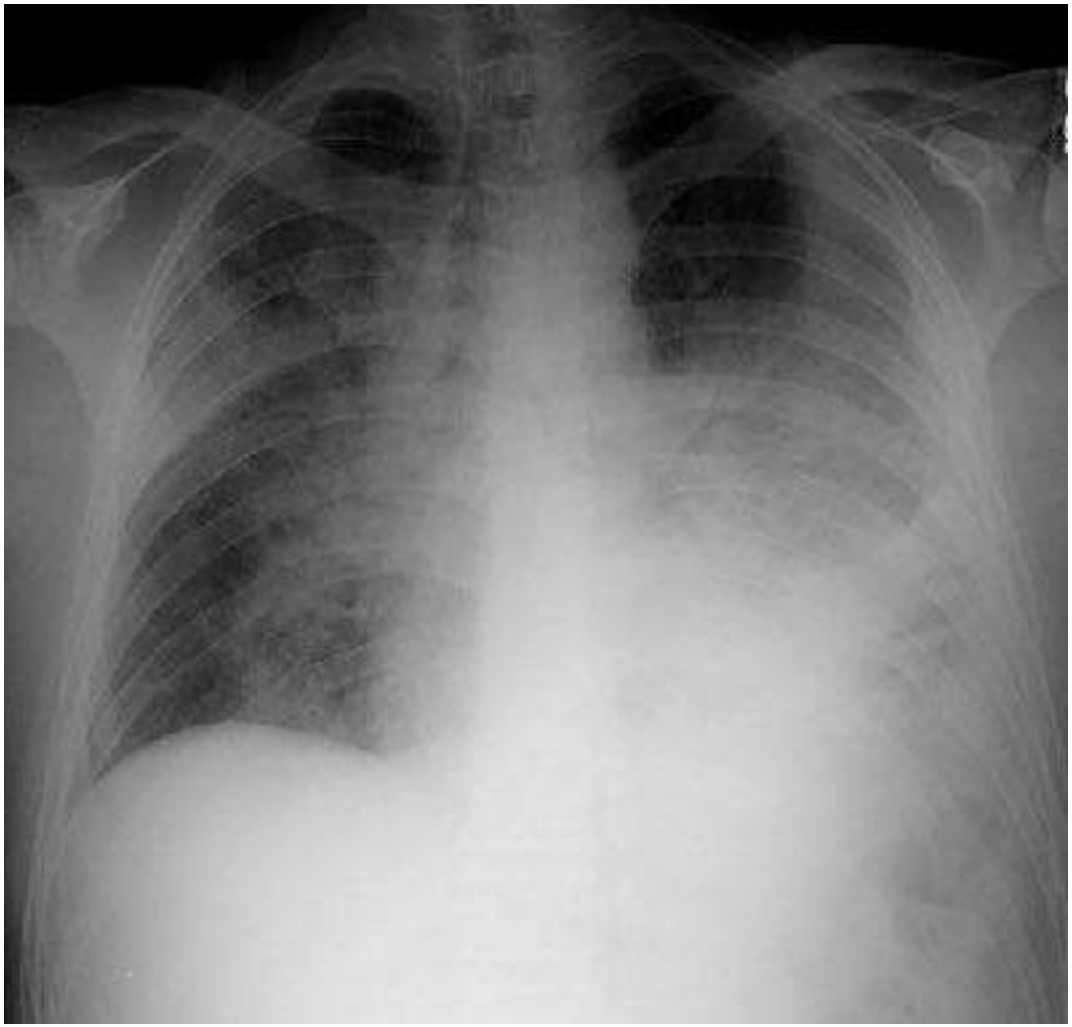
Peritonsillar abscess



Lin YY et al. CMAJ 2011;183:1276

Group A streptococcal pneumonia

- early appearance of pleural effusion and evolution to empyema



Acute Rheumatic Fever

- Paradigm of nonsuppurative GAS complication
- Multisystem involvement:
- Major manifestations: carditis, migratory polyarthritis, chorea, subcutaneous nodules and erythema marginatum
- Minor manifestations: fever, arthralgia, first degree heart block, acute-phase reactions (elevated ESR, CRP)

➢ Latency period following GAS pharyngitis is 19 days (10-35 days)

➢ May present with multiple concurrent or sequential manifestations

➢ **The use of long term antibiotics for the prevention of recurrent acute rheumatic fever is the foundation for antibiotic therapy in PANDAS**

Poststreptococcal glomerulonephritis

- No reliable markers to distinguish nephritogenic vs. nonnephritogenic strains
- Presumed immunologic mechanism:

➢ 7 day latency period

➢ associated hypocomplementemia

➢ Presence of IgG, complement and streptococcal antigens in glomeruli

➢ Seasonal pattern associated with pyoderma incidence

➢ Attack rate 10-15%, recurrence rare

➢ Classic features: edema, rust-colored urine, hypertension

➢ Anti-DNase B titers more robust for diagnosis than ASLO

Thomas Sydenham, 1624-1689
"The English Hippocrates"

He first reported febrile polyarthritis in 1685

He first reported observing chorea in 1686, and noted behavioral changes in children with chorea

Association of chorea with juvenile rheumatism

GAS/Acute Rheumatic Fever: >325 years of progress

- Association of valvular lesions with childhood rheumatism 1797
- Identification of streptococci 1874 (Bilroth)
- Speciation of group A streptococci 1918
- Role of antecedent infection identified in early 1940s:

Pharyngitis, antecedent respiratory tract infection, and infections by hemolytic streptococci preceded bouts of acute rheumatic fever.

- Progress in development of penicillin/penicillin prophylaxis

Gerber MA et al.
Circulation 2009;119:1541

Table 3. Duration of Secondary Rheumatic Fever Prophylaxis

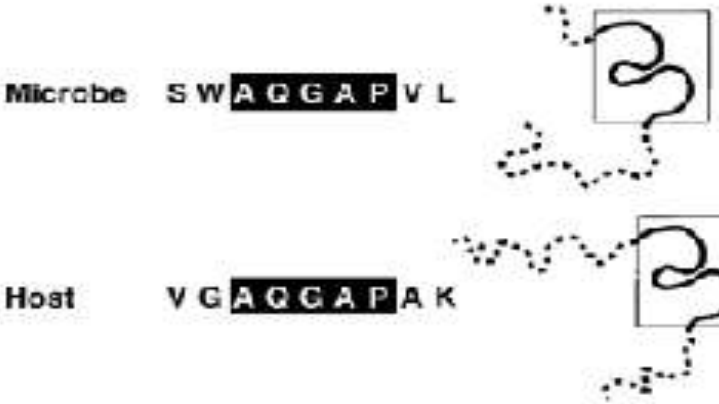
Category	Duration After Last Attack	Rating
Rheumatic fever with carditis and residual heart disease (persistent valvular disease*)	10 years or until 40 years of age (whichever is longer), sometimes lifelong prophylaxis (see text)	IC
Rheumatic fever with carditis but no residual heart disease (no valvular disease*)	10 years or until 21 years of age (whichever is longer)	IC
Rheumatic fever without carditis	5 years or until 21 years of age (whichever is longer)	IC

GAS/Acute Rheumatic Fever

Why does group A streptococcal pharyngitis lead to the development of acute rheumatic fever (and/or other nonsuppurative complications?)

Molecular mimicry links infection to autoimmunity

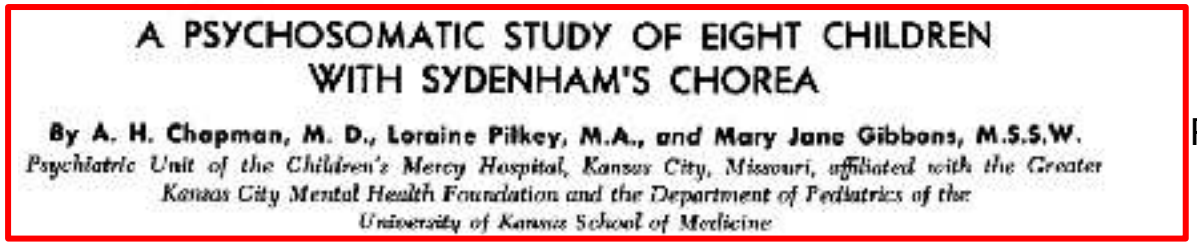
- Microorganisms rather frequently have proteins that share immunologically distinct structural features (“epitopes”) with host proteins (“cross – reactive epitopes”).
- Immune responses against microorganisms that express these shared epitopes can recognize host structures with resultant **autoimmunity.**



Oldstone M. FASEB J 1998;12:1255

- **Molecular [illegible] suppurative complications of GAS infection. GAS-specific Abs can cross-react with basal ganglia neurons**

OCD: PSYCHIATRIC SEQUELA OF GAS INFECTION

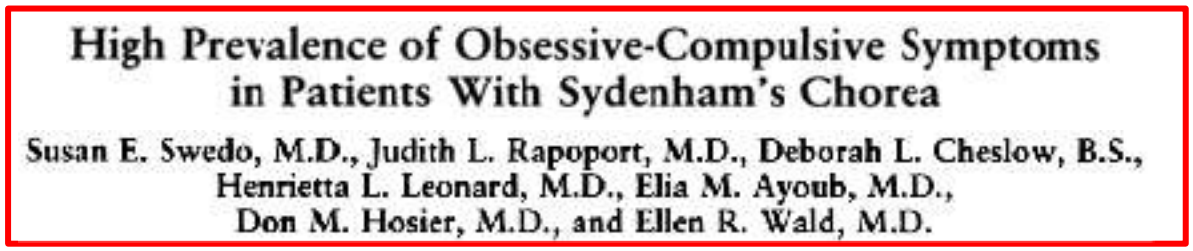


A PSYCHOSOMATIC STUDY OF EIGHT CHILDREN WITH SYDENHAM'S CHOREA

By A. H. Chapman, M. D., Loraine Pilkey, M.A., and Mary Jane Gibbons, M.S.S.W.

Psychiatric Unit of the Children's Mercy Hospital, Kansas City, Missouri, affiliated with the Greater Kansas City Mental Health Foundation and the Department of Pediatrics of the University of Kansas School of Medicine

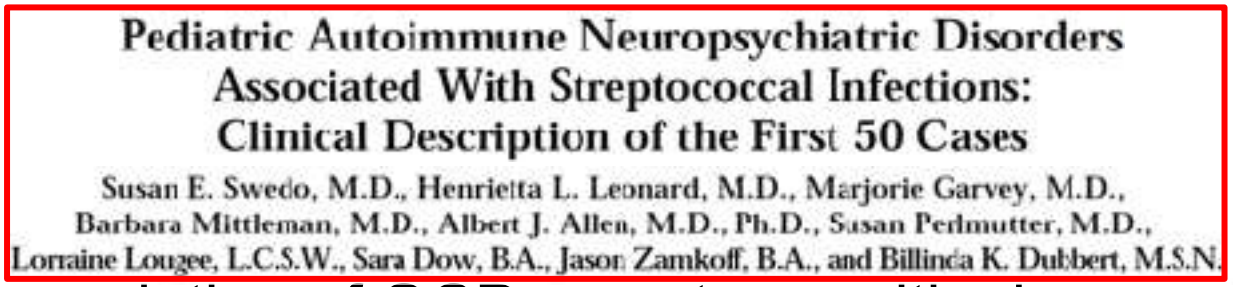
Pediatrics 1958; 21:582



High Prevalence of Obsessive-Compulsive Symptoms in Patients With Sydenham's Chorea

Susan E. Swedo, M.D., Judith L. Rapoport, M.D., Deborah L. Cheslow, B.S., Henrietta L. Leonard, M.D., Elia M. Ayoub, M.D., Don M. Hosier, M.D., and Ellen R. Wald, M.D.

Am J Psychiatry 1989; 146: 246



Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections: Clinical Description of the First 50 Cases

Susan E. Swedo, M.D., Henrietta L. Leonard, M.D., Marjorie Garvey, M.D., Barbara Mittleman, M.D., Albert J. Allen, M.D., Ph.D., Susan Perlmutter, M.D., Lorraine Lougee, L.C.S.W., Sara Dow, B.A., Jason Zamkoff, B.A., and Billinda K. Dubbert, M.S.N.

Am J Psychiatry 1998; 155:264

- the association of OCD symptoms with chorea suggests basal ganglia inflammation is linked to behavior

EPIDEMIOLOGIC/CLINICAL FEATURES OF PANDAS

Age at onset: ~7 +/- 3 y; males predominate (60-70%)
Associated GAS infection high in published series (~80%)

- **Prepubertal onset (typically)**
- **Acute onset of symptoms; relapsing/remitting course**
- **Presence of OCD symptoms/eating disorder or tics**
- **Associated neurologic abnormalities (tics, choreiform movements)**
- **Temporal association with GAS infection**

PANDAS ASSOCIATED SYMPTOMS/SIGNS

Anxiety (especially separation anxiety) (73-95%)

Emotional lability and/or depression ("**meltdowns**") (66-94%)

Irritability, aggressive and/or oppositional behaviors (26-50%)

Sensory/motor abnormalities including tics (77-97%)

Somatic signs/symptoms, including sleep disturbance, **enuresis, urinary frequency** (83-98%)

Deterioration in school performance (75-88%)

Behavioral regression (60-69%)

Chang K et al. J. Child Adolesc Psychopharm 2015;25:3
Swedo SE et al. J Child Adolesc Psychopharm 2015;25:26

ADDITIONAL COMMONLY REPORTED FEATURES

TABLE 3. COMPARISON OF CLINICAL CHARACTERISTICS OF PANDAS PATIENTS IN COMMUNITY AND RESEARCH SETTINGS

	NIMH (n = 48)		*Community* (n = 72)		
	#	%	#	%	χ^2
Separation anxiety	44	92%	62	86%	NS
Behavioral regression (tantrum, baby talk)	30	63%	47	65%	NS
OCD symptoms	48	100%	72	100%	NS
Intrusive thoughts	19	40%	53	74%	NS
Phobias/contamination fears	40	83%	40	56%	NS
Unfounded fears	24	50%	48	67%	NS
Repetitive behaviors	36	75%	39	54%	NS
Aggressiveness	20	42%	26	36%	NS
Hyperactivity or inattentiveness	44	92%	34	47%	4.5 (p=0.03)
Violent images or hallucinations	13	27%	10	14%	NS
Dysgraphia	21	44%	46	64%	NS
Mydriasis	16	33%	45	63%	NS
Tics	32	67%	43	60%	NS
Urinary symptoms	25	52%	58	81%	NS
Frequency and/or urgency	14	29%	40	56%	NS
Daytime or night-time enuresis	9	19%	33	46%	NS
Increased sensory sensitivity	21	44%	31	43%	NS
School issues	39	81%	54	75%	NS
Inability to concentrate	38	79%	47	65%	NS
Trouble in math	16	33%	30	42%	NS
Sleep problems	34	71%	51	71%	NS
Restricted food intake	23	48%	17	24%	NS

Swedo SE et al. J Child Adolesc Psychopharm 2015;25:26.

Molecular mimicry may explain the nonsuppurative complications of GAS infection

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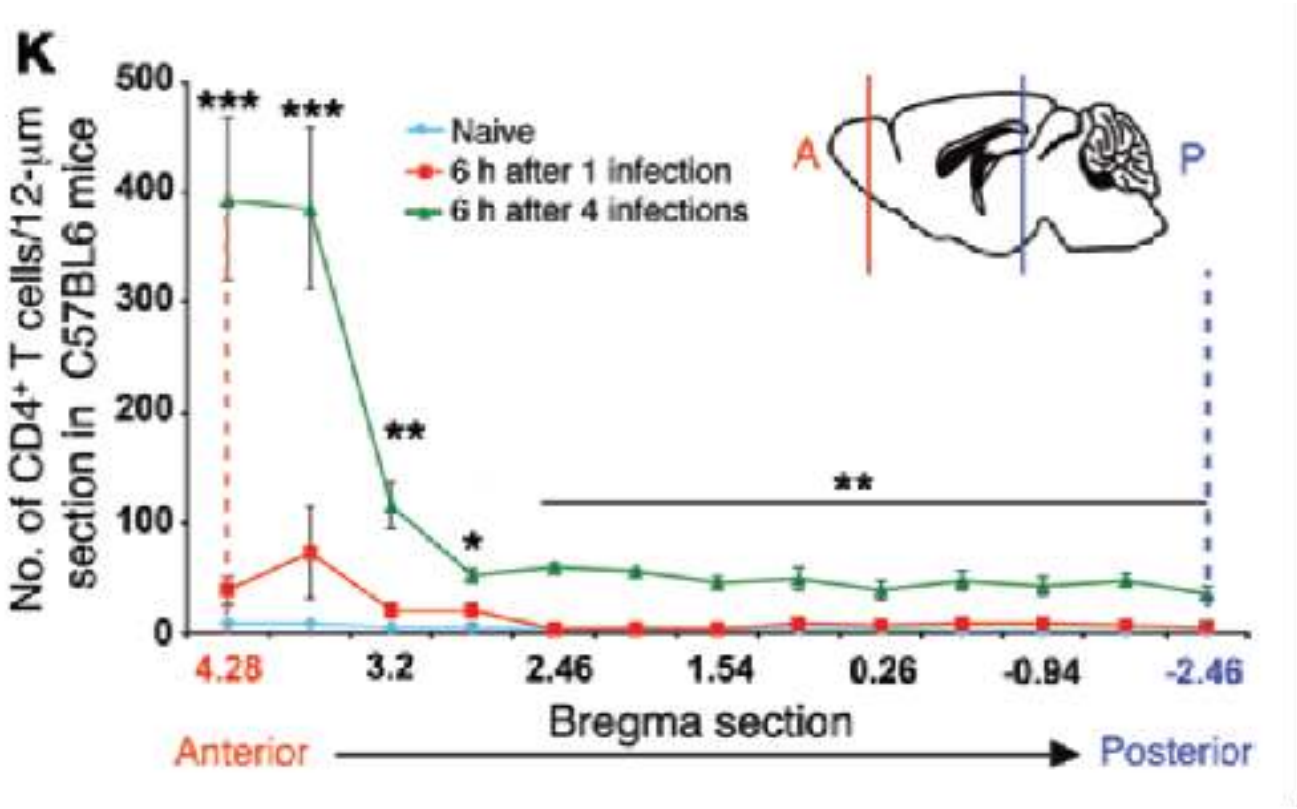
Lymphocytes selectively infiltrate the brains of mice following repeated intranasal inoculation

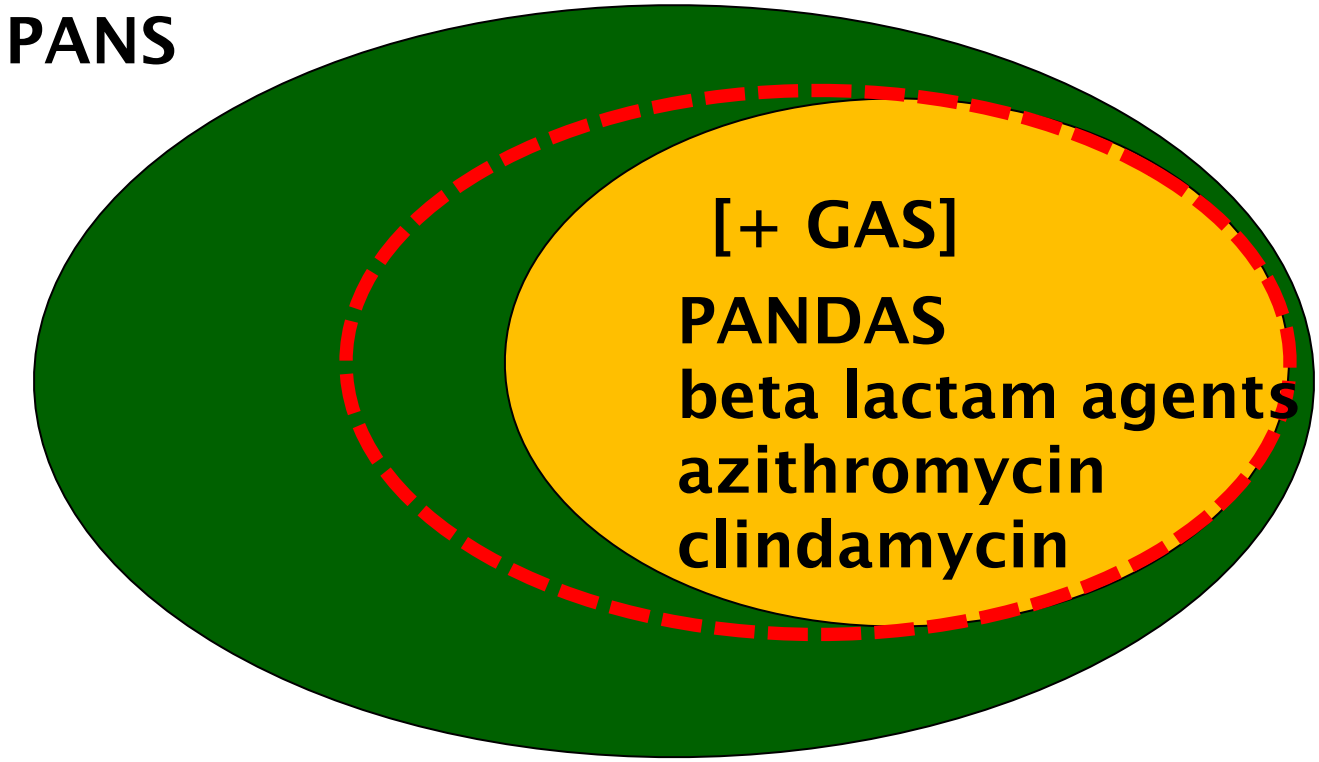


Dileepan T et al. J Clin Invest 2016;126(1):303–317

The challenge of PANDAS vs. PANS

- What is PANS? What is PANDAS?
- Are the challenges of accurate microbiologic diagnosis worthwhile? Etiology guides therapy…

[- GAS]→azithromycin, doxycyline



Many unresolved problems …

- Diagnosis of group A strep infection
- Limitations of microbial diagnosis
- Limitations of serologic diagnosis
- Limitations of therapy (targeted and empiric therapies)

Diagnostic and Therapeutic Challenges: PANS vs. PANDAS

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- Operational challenges: the distinction between PANS and PANDAS **is a clinical and microbiologic challenge**

  - challenges in diagnosis (PANDAS vs. PANS) by rapid testing/culture – **importance of timing of laboratory investigation**

  - importance of detailed clinical history and appropriate laboratory investigation re: alternate triggering infections (Mycoplasma, influenza, SARS CoV2, Lyme, HSV, etc.)

  - challenges in serologic monitoring as measure of antibiotic efficacy - **this is imperfect technology**

  - apparent failures of penicillin VK / amoxicillin? ***Why?***

  - Discrepancies between ARF and PANDAS antibiotic dosing

  - role of second line GAS agents: cephalosporins, amoxicillin/ clavulanate, azithromycin, clindamycin, IM benzathine PCN

  - role of alternate therapies: doxycycline, valacyclovir

Laboratory evaluation

- Look for GAS, especially in previously untreated patients:

  Throat culture / [consider] rectal swab, especially in younger children or those with a history of perianal rash/pruritis

  More difficult diagnostic challenges: sinusitis, impetigo, guttate psoriasis

- Serology:

  -- Anti-streptolysin O; Anti-DNase B

  – Mycoplasma pneumoniae IgG, IgM (with confirmatory IFA testing)

  – Other relevant testing when appropriate: Lyme disease, etc.

  Challenge of timing of evaluation relative to onset of symptoms

  Limitations of traditional and conventional GAS serology

  -- Immunologic screening: IgG, A, M; IgG subclass levels; S. pneumoniae Ab panel

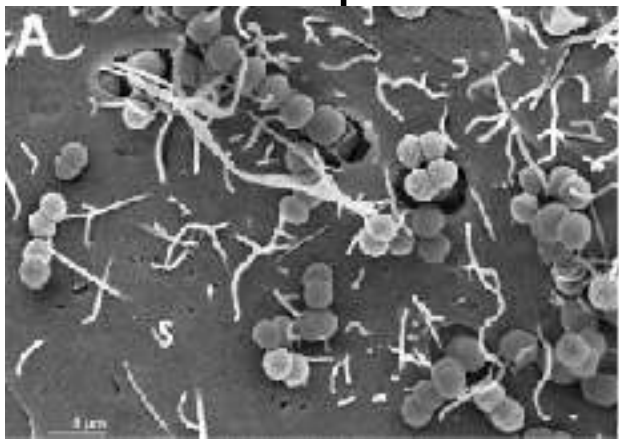
  -- Autoimmunity screening: ANA, TSH, TPO

Complexities in GAS pathogenesis:

- Implications for culture – negative pharyngitis? **False neg. vs. true neg.**
- Heightened rates of amoxicillin failure in the therapy of GAS pharyngitis– likely due to amoxicillin degradation by beta-lactamases secreted by oral flora→increasing need for cephalexin
- Beta lactam agents cannot penetrate the apical epithelial cell membrane to interact with sequestered (intracellular) streptococci, which may contribute to treatment failure
- Implications for preferential use of azithromycin for suppression? ***But*** rising rates of azithromycin resistance (>20%)

COMPLEXITIES IN GAS PATHOGENESIS: WHY IS IT HARD TO DOCUMENT ROLE OF GAS?

GABHS superficially invades epithelial surfaces (tonsillar, pharyngeal epithelium) ***but can establish persistent intracellular infection*** in epithelial cells



In: Rohde M, Cleary PP. Adhesion and invasion of *Streptococcus pyogenes* into host cells and clinical relevance of intracellular streptococci. 2016 Feb 10. Ferretti JJ, Stevens DL, Fischetti VA, eds. *Streptococcus pyogenes : Basic Biology to Clinical Manifestations [Internet]. Oklahoma City (OK): University of Oklahoma Health Sciences Center; 2016*]

Centor Criteria for treatment of suspected bacterial pharyngitis

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Centor criteria (1 point for each)
Fever
Tonsillar exudates
Anterior cervical lymphadenopathy
Absence of cough
Age <15 years (McIsaac adjustment)

Centor score	Probability of streptococcal infection	Suggested management
1	~1-17% – low	No antibiotics
2	10-23% – low	No antibiotics
3	17-23% – intermediate	Consider antibiotic treatment
4	35-50% – intermediate	Consider antibiotic treatment
5	51-68% – high	Empirical treatment with antibiotics

Notes: The McIsaac adjustment adapts for the patient's age adding one point for <15 years, and subtracting one point for >45 years. Probability of streptococcal infection data are from Fine *et al.* (2012), McIsaac *et al.* (2004). Suggested management is based on NICE (2008), SIGN (2010)

Fine AM et al. Int J Health Care Qual Assur. 2017;30:319-326.

es in diagnosis?

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lemiological Findings and Diagnosis nosis

Features suggestive of GAS as causative agent	Features suggestive of viral origin
Sudden-onset sore throat	Conjunctivitis
Pain on swallowing	Coryza
Fever	Hoarseness
Scarlet fever rash	Cough
Headache	Diarrhea
Nausea, vomiting, and abdominal pain	Characteristic exanthems
Tonsillopharyngeal erythema	Characteristic enanthems
Tonsillopharyngeal exudates	
Soft palate petechiae ("doughnut" lesions)	
Beefy, red, swollen uvula	
Tender, enlarged anterior cervical nodes	
Patient 5 to 15 years of age	
Presentation in winter or early spring (in temperate climates)	
History of exposure	

Gerber MA et al. Circulation 2009;119:1541

GAS pearls – Dr. Gene Stollerman (1961)

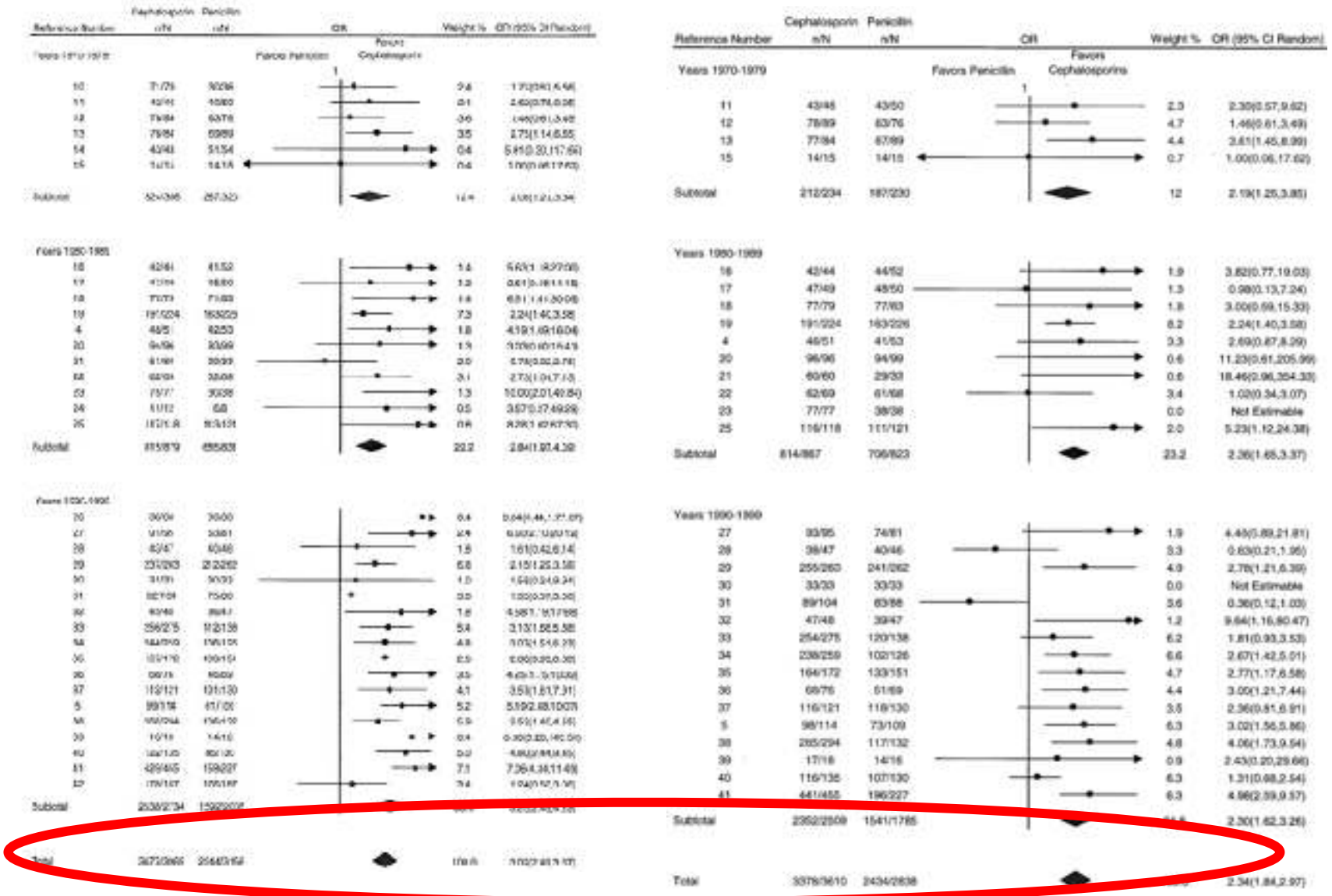
infection. It should be emphasized again that *only streptococcal infections which were associated with significant antibody responses produced rheumatic fever.* Throat carriage of streptococci in asympto-

. In other words, about two-thirds of streptococcal infections associated with an antibody rise may occur as subclinical infections. Are all such infections of equal danger to the rheumatic host?

Simply stated, the diagnosis of clinically significant GAS pharyngitis (based on titer rise) is inherently challenging

Stollerman GH. JAMA 1961;177:843

Cephalosporins vs. Penicillin for therapy of GABHS tonsillopharyngitis



Casey JR and Pichichero ME. Pediatrics 2004;113:866

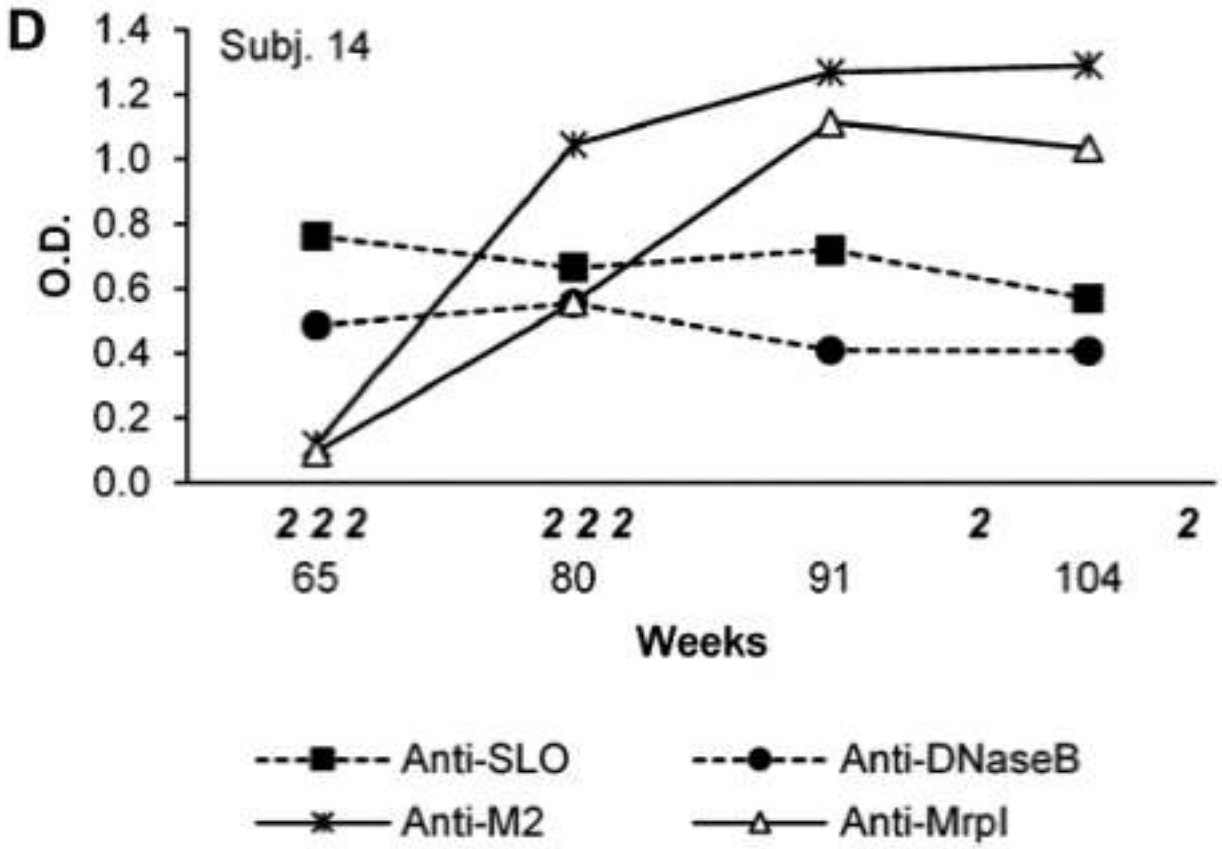
Rising rate of erythromycin and clindamycin resistance among GAS

Table 1: GAS Susceptibilities (n=143)

	Erythromycin	Clindamycin
Susceptible	85%	85%
Intermediate	1%	2%
Resistant	14%	13%
Total non-susceptible	15%	15%

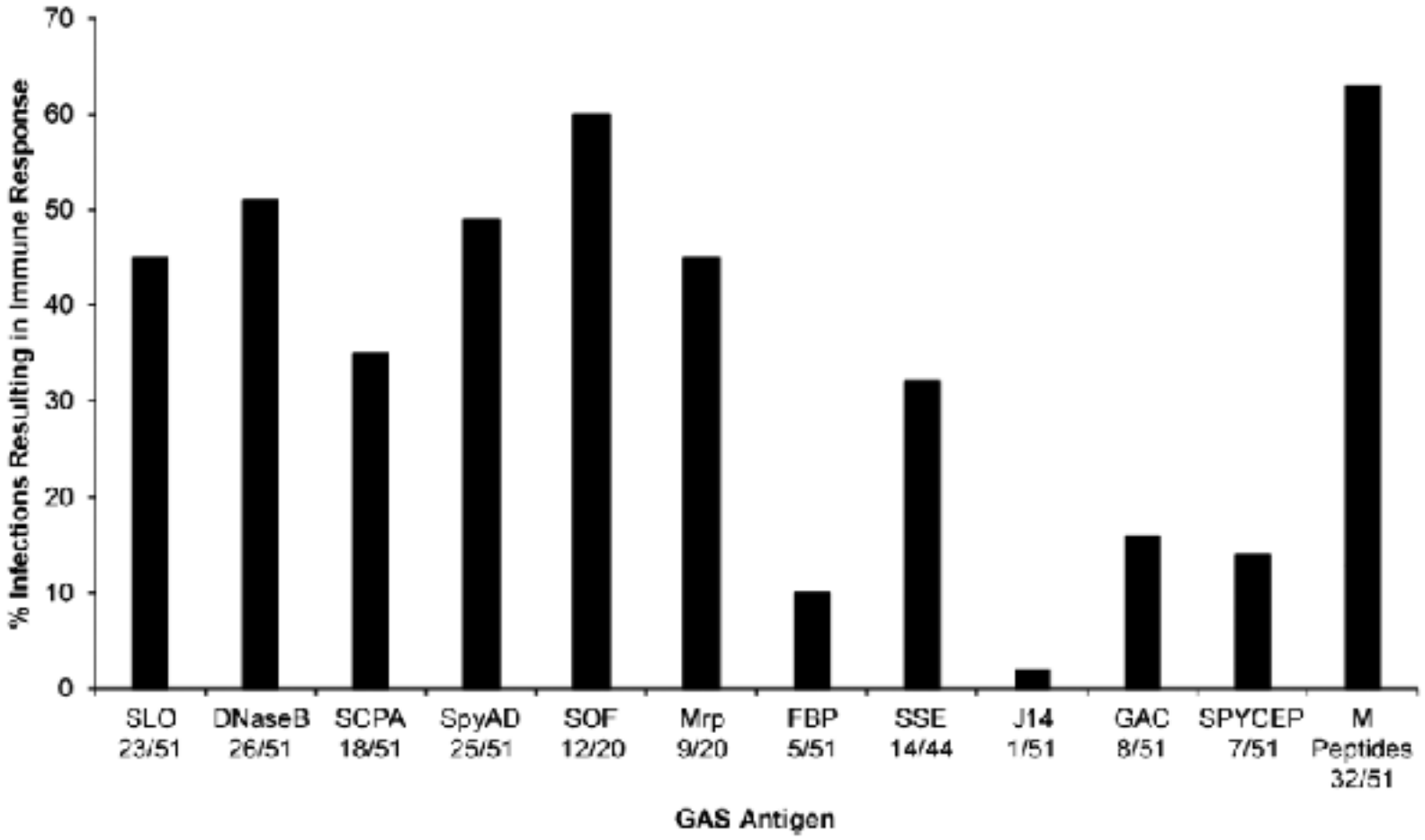
DeMuri GP et al. Pediatr Infect Dis J 2016; 11/28/16 Epub

Limitations of classic ASO, anti-DNase B testing



Hysmith ND, et al. J Pediatr Infect Dis Soc 2017:6:187

Immune response to individual GAS antigens is incomplete



Hysmith ND, et al. J Pediatr Infect Dis Soc 2017;6:187

How did we come to use antibiotics to treat pediatric OCD/tics?

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AHA guidelines for secondary prevention of Rheumatic Fever [prophylaxis—analogous to PANDAS Rx]

Table 3. Duration of Secondary Rheumatic Fever Prophylaxis

Category	Duration After Last Attack	Rating
Rheumatic fever with carditis and residual heart disease (persistent valvular disease*)	10 years or until 40 years of age (whichever is longer), sometimes lifelong prophylaxis (see text)	IC
Rheumatic fever with carditis but no residual heart disease (no valvular disease*)	10 years or until 21 years of age (whichever is longer)	IC
Rheumatic fever without carditis	5 years or until 21 years of age (whichever is longer)	IC

Table 4. Secondary Prevention of Rheumatic Fever (Prevention of Recurrent Attacks)

Agent	Dose	Mode	Rating
Benzathine penicillin G	600 000 U for children ≤27 kg (60 lb), 1 200 000 U for those >27 kg (60 lb) every 4 wk*	Intramuscular	IA
Penicillin V	250 mg twice daily	Oral	IB
Sulfadiazine	0.5 g once daily for patients ≤27 kg (60 lb), 1.0 g once daily for patients >27 kg (60 lb)	Oral	IB
For individuals allergic to penicillin and sulfadiazine			
Macrolide or azalide	Variable	Oral	IC

How did we come to use antibiotics to treat pediatric OCD/tics?

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- Role of antibiotic prophylaxis in the management of acute rheumatic fever
- Role of antibiotic prophylaxis in the management of Sydenham's chorea (SC)
- Recognition of PANDAS as a possible overlap syndrome with SC with a similar "molecular mimicry" hypothesis underlying neurologic manifestations of disease ⟶ Antibiotic prophylaxis for PANDAS
- Recognition of non-GABHS – associated acute onset pediatric OCD
- Classification of PANDAS as a subset of a broader disease process – PANS
- **Implications for selecting antibiotic prophylaxis/suppression**

AHA/AAP guidelines for treating acute GAS pharyngitis

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TABLE 2. ANTIMICROBIAL TREATMENT OF ACUTE STREPTOCOCCAL PHARYNGITIS

Agent, route, duration	*Dose, frequency*	*Rating*[a]
Penicillin V po × 10 days	Children: 250 mg/dose bid or tid; Adolescents or adults: 500 mg/dose bid	Strong, high
Amoxicillin po × 10 days	50 mg/kg once daily, maximum 1 g	Strong, high
Benzathine penicillin G im once	≤27 kg (60 lb): 600,000 U >27 kg (60 lb): 1.2 M U	Strong, high
	If penicillin-allergic	
Cephalexin[b] po × 10 days	20 mg/kg/dose bid, maximum 500 mg/dose	Strong, high
Cefadroxil[b] po × 10 days	30 mg/kg once daily, maximum 1 g	Strong, high
Clindamycin po × 10 days	7 mg/kg/dose tid, maximum 300 mg/dose	Strong, moderate
Azithromycin po × 5 days	12 mg/kg once, maximum 500 mg, then 6 mg/kg daily, maximum 250 mg, for 4 days	Strong, moderate
Clarithromycin po × 10 days	7.5 mg/kg/dose bid, maximum 250 mg/dose	Strong, moderate

American Heart Association, American Academy of Pediatrics (adapted from Shulman et al. 2012).
[a]Strength of recommendation, level of evidence (as detailed in Shulman et al. 2012).
[b]Avoid with immediate (type I) hypersensitivity to a penicillin.
bid, twice daily; tid, three times daily; po, per os; im, intramuscular.

Cooperstock M et al. J Child Adolesc Psychopharm 2017; 27:594

Antibiotic Prophylaxis

- Many PANDAS children experience relapsing symptoms/flares with conventional acute rheumatic fever prophylaxis recommendations. **Possible explanations:**

➢ Beta lactamase producing oral flora

➢ Reduced antibiotic absorption (compliance usually excellent)

➢ Sequestered infection (?intratonsillar abscesses, ?intracellular persistence)

➢ It is common to use **therapy-level dosing regimens for prophylaxis**

➢ e.g., cephalexin or amoxicillin/clavulanate at 40-50 mg/kg/d div b.i.d. for long term prophylaxis—even then, occasional +throat swabs seen

➢ Caveats: cefadroxil once daily therapy has higher breakthrough rate

➢ Macrolides (5-10 mg/kg/d) and clindamycin (5-10 mg/kg/d div 3id) are associated with 20%+ failures–challenge for β-lactam allergic children

➢ Rifampin (10-20 mg/kg/d, ≤600 mg/d) occasionally helpful re: synergy and benzathine penicillin occasionally helpful if compliance issues

Hypervirulent M1T1 Group A streptococci

- In the 1980s a new clone of M1T1 GAS was recognized, and has been widely distributed.
- In contrast to prior M1T1 clones (a common serotype), this clone was **hypervirulent**
- The hypervirulent M1T1 clone was frequently responsible for life-threatening infections:

➢ necrotizing fasciitis (“flesh-eating bacteria”)

➢ Streptococcal toxic shock syndrome

- The molecular basis for this enhanced virulence is complicated:

2 bacteriophages (bacterial viruses) introduced genes for increased expression of a pyrogenic exotoxin (speA) and decreased expression of a DNA degrading enzyme (sda1). The expression of these factors is regulated dynamically, thus modulating the virulence of the strain depending on host and growth circumstances