Update on microbiological aspects of *Streptococcus pyogenes* infections

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Overview

- Microbiology and spectrum of GAS infections
- What makes GAS a pathogen?
- Why is GAS ‘always’ susceptible to penicillin?
- Why do some people ‘fail’ treatment?
- How do we classify GAS infections?
- Are there ‘rheumatogenic’ GAS strains?

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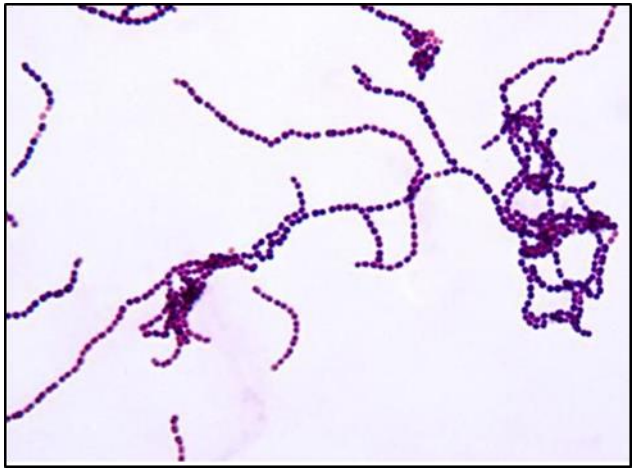
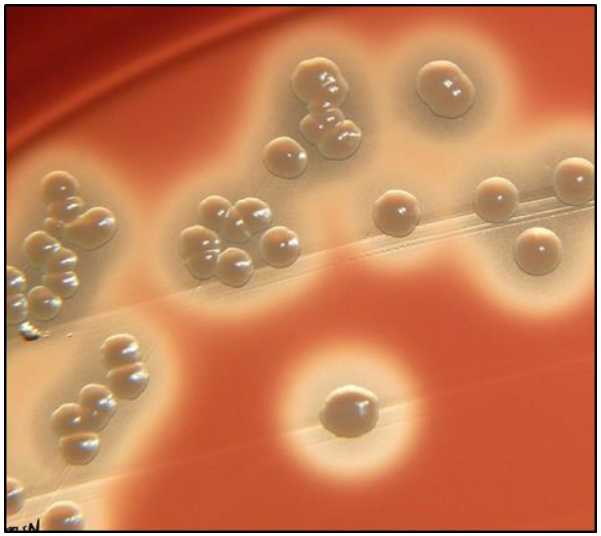
GAS microbiology: The basics

- '*Streptos*': twisted chain
- '*Cocci*': round bacteria
- Sole member of Lancefield group A
- Causes marked haemolysis on blood agar
- Incubation period in the laboratory 18-36 hours





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Spectrum of GAS infections

- **Superficial**
  - Impetigo (>110 million cases per year)
  - Pharyngitis (>600 million cases per year)
  - Scarlet fever (speA)
- **Immune sequelae**
  - ARF / RHD
  - Post-streptococcal glomerulonephritis (PSGN)
  - PANDAS
- **Invasive disease**
  - Bacteraemia
  - Deep skin infection
  - Necrotising fasciitis
  - Septic arthritis
  - And others……

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What makes GAS a pathogen?

- Colonisation, adhesion and invasion of host epithelial cells
  - e.g. pilus; Fbp's; Lbp
- Evasion of immune system
  - E.g. M protein; SLO; capsule
- Survival and growth in blood
  - e.g. SpeB
- Secretion of virulence factors
  - E.g. SpeA

Why is GAS always susceptible to penicillin?

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 1982, p. 128–136 Vol. 22, No. 1
0066-4804/82/070128-09$02.00/0

Penicillin-Resistant and Penicillin-Tolerant Mutants of Group A Streptococci

LAURENT GUTMANN AND ALEXANDER TOMASZ*
The Rockefeller University, New York, New York 10021

Received 19 February 1982/Accepted 28 April 1982

Penicillin-resistant and penicillin-tolerant mutants have been isolated from group A streptococci mutagenized by ethyl methane sulfonate. The resistant mutants had an elevated minimal growth inhibitory concentration for benzylpenicillin (minimal inhibitory concentration, 0.2 μg/ml, as compared with the minimal inhibitory concentration of 0.006 μg/ml in the penicillin-susceptible parent strain); they also had an abnormal cellular morphology and showed altered penicillin-binding proteins. Penicillin-tolerant mutants were killed more slowly than were the parental cells during treatment with penicillin; they had virtually unchanged minimal inhibitory concentration values for penicillin and normal cellular morphology and penicillin-binding proteins.

Why Have Group A Streptococci Remained Susceptible to Penicillin? Report on a Symposium*

David L. Horn and John B. Zabriskie, chairpersons, and the following participants: Robert Austrian, P. Patrick Cleary, Joseph J. Ferretti, Vincent A. Fischetti, Emil Gotschlich, Edward L. Kaplan, Maclyn McCarty, Steven M. Opal, Richard B. Roberts, Alexander Tomasz, and Yanina Wachtfogel

From Merck & Co., Inc., West Point, Pennsylvania; Rockefeller University, New York, New York; University of Pennsylvania, Philadelphia, Pennsylvania; University of Minnesota, Minneapolis, Minnesota; University of Oklahoma, Oklahoma City, Oklahoma; Brown University School of Medicine, Providence, Rhode Island; and Department of Medicine, The New York Hospital/Cornell Medical Center, New York, New York

Clinical Infectious Diseases 1998;26:1341–5

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Why is GAS always susceptible to penicillin?

- Inefficient mechanisms for genetic transfer
- Barriers to DNA uptake
  - GAS produce at least 4 extracellular DNAase
  - Have RM systems
  - Not naturally competent
- Beta-lactamase may not be expressed or may be toxic to GAS
- Low affinity PBPs may impose a critical fitness cost

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Why is GAS always susceptible to penicillin?

NZ, 2015:

Table 4. Penicillin MIC distribution, and erythromycin and clindamycin resistance, among *S. pyogenes* from children in RFPP district health boards compared with South Island children

Source of isolates	% of isolates with a penicillin MIC (mg/L) of:			% resistance	
	0.008	0.016	0.03	erythromycin	clindamycin
Children from school-based sore throat management programmes (*n* = 100)	0.0	100	0.0	0.0	0.0
Children in South Island DHBs (*n* = 103)	1.0	91.3	7.8	5.8[1]	5.8[1]

1 All erythromycin-resistant isolates also demonstrated constitutive clindamycin resistance. No inducible clindamycin resistance was detected.

ESR

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Why does GAS sometimes ‘fail’ treatment with penicillin?

- Enters epithelial cells, which are poorly penetrated by penicillin
- Forms a biofilm on the oropharynx
- Another anatomical niche?
- Protection by beta-lactamase production from other species (never proven)

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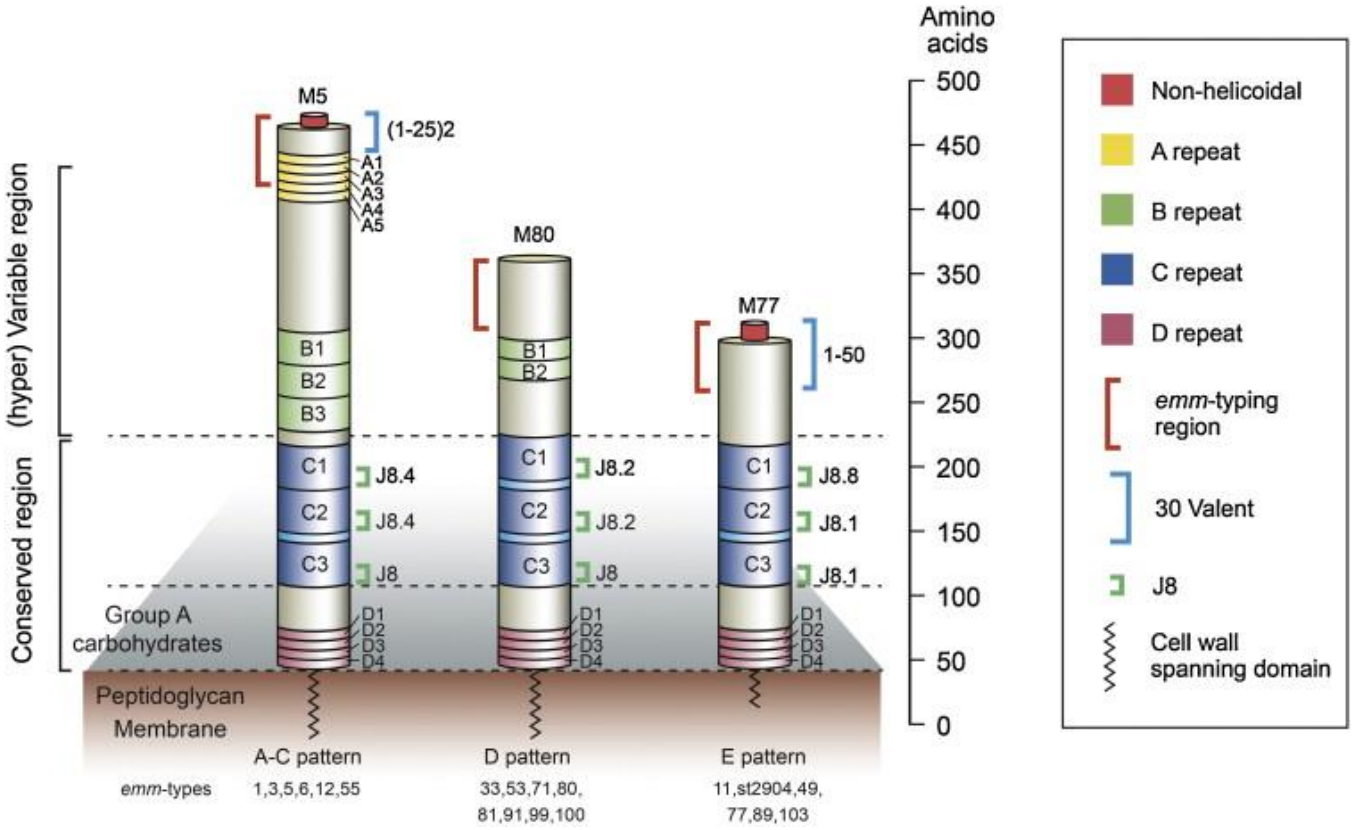
Classifying GAS infections – *emm* typing



Moreland et al., Vaccine, 2014

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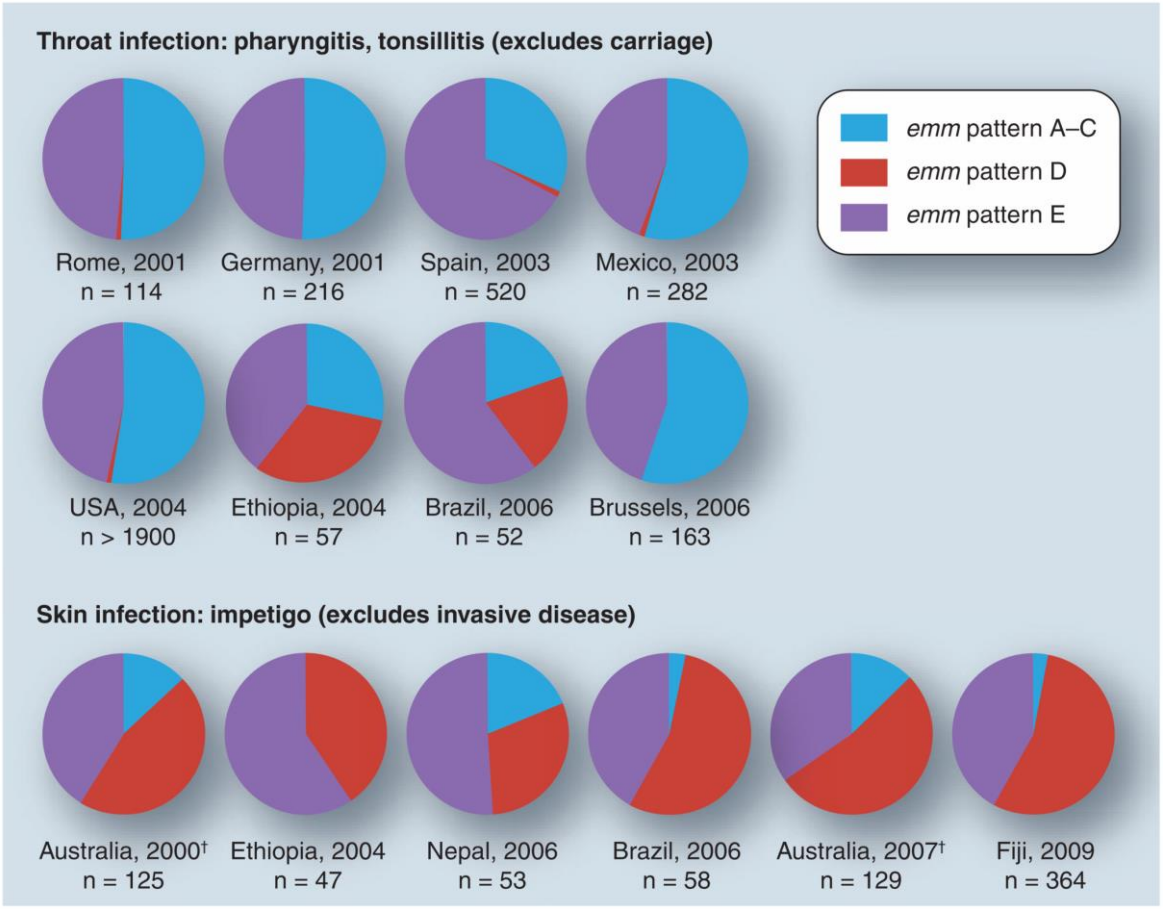
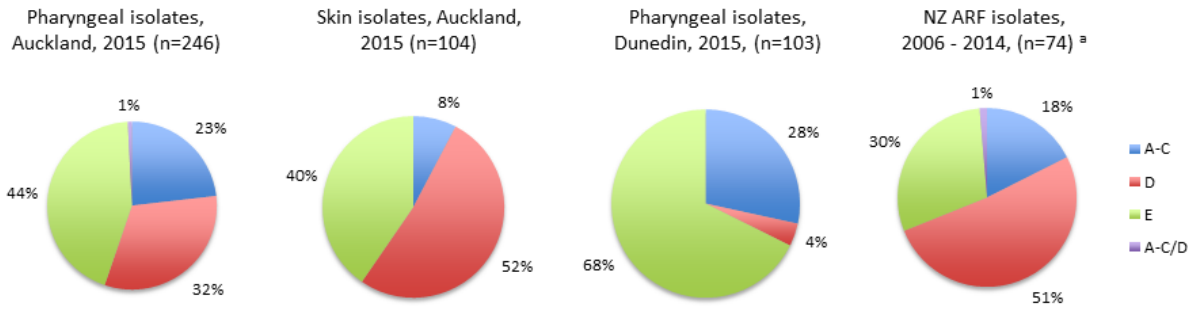
Tissue tropism and GAS infection



Tissue tropism and GAS infection, NZ



Williamson et al., JCM, 2015
Williamson et al., submitted

Theoretical vaccine coverage (30-valent)

	Pharyngeal GAS isolates, Auckland; n=246 (95% CI)	Skin GAS isolates, Auckland; n=104 (95% CI)	Pharyngeal GAS isolates, Dunedin; n=103 (95% CI)
Theoretical 30-valent coverage	48.4% (42.2% – 54.6%)	33.7% (25.3%– 43.2%)	93.2% (86.4% - 96.9%)
Theoretical additional coverage with cross-opsonic effect [a]	69.5% (63.4% – 74.9%)	54.8% (45.2% – 64.0%)	95.1% (88.9% - 98.2)
Proportion of isolates belonging to *emm* types not tested for cross-opsonic effect [a]	27.6% (22.4% - 33.6%)	38.5% (29.7% - 48.1%)	2.9% (0.6% - 8.6%)

Submitted

Are there ‘rheumatogenic’ strains of GAS?

Crucial Role of the CB3-Region of Collagen IV in PARF-Induced Acute Rheumatic Fever

PLoS ONE | www.plosone.org

March 2009 | Volume 4 | Issue 3 | e4666

TABLE 2 PARF motifs detected in group A *Streptococcus* isolates from New Zealand

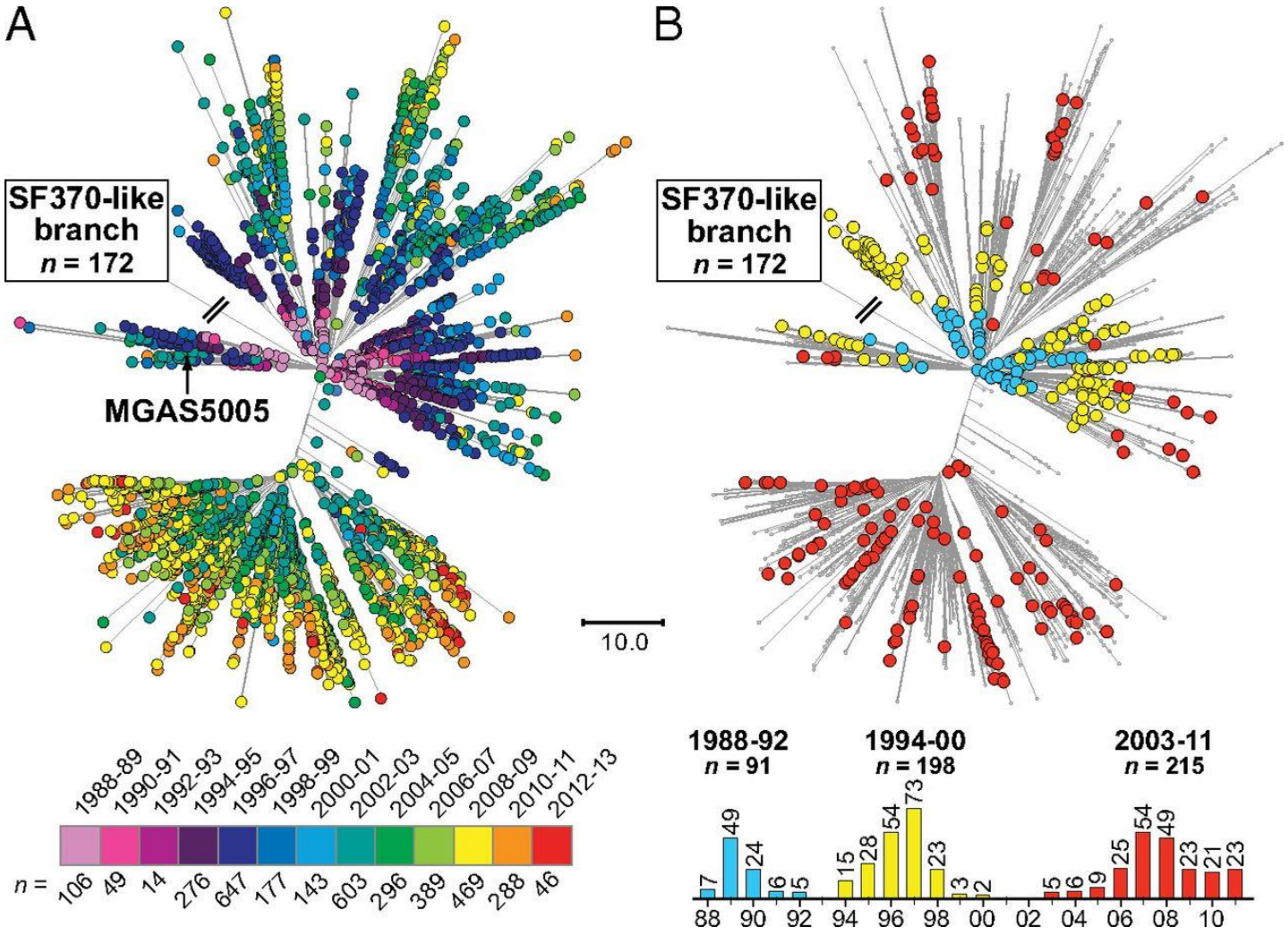
emm type (*n*)	*emm* cluster	PARF motifs (no. associated with each *emm* type)
*emm*3 (40)[a]	A-C5	AEYLKSLN (34)[a]; AEYLKGLN (4); AEYLKGFN (2)
*emm*31 (2)	A-C5	AEYLKALN (1); AEYLKGLN (1)
*emm*55 (5)	*emm* cluster M55	ATYLKELN (5)
*emm*222 (2)	*emm* cluster M222	ANYLKELN (2)

[a] Includes one ARF-associated strain.

n=2,999

Williamson et al., JCM, 2015

What does the future hold for GAS microbiology?



Waleed Nasser et al. PNAS 2014;111:E1768-E1776

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Summary

- GAS infections are due to a complex interplay between host, bacteria and environment
- Penicillin continues to be a first-line treatment
- Classification of GAS infections is likely to undergo major changes in the next 5 years
- WGS promises new insights into the understanding of GAS disease