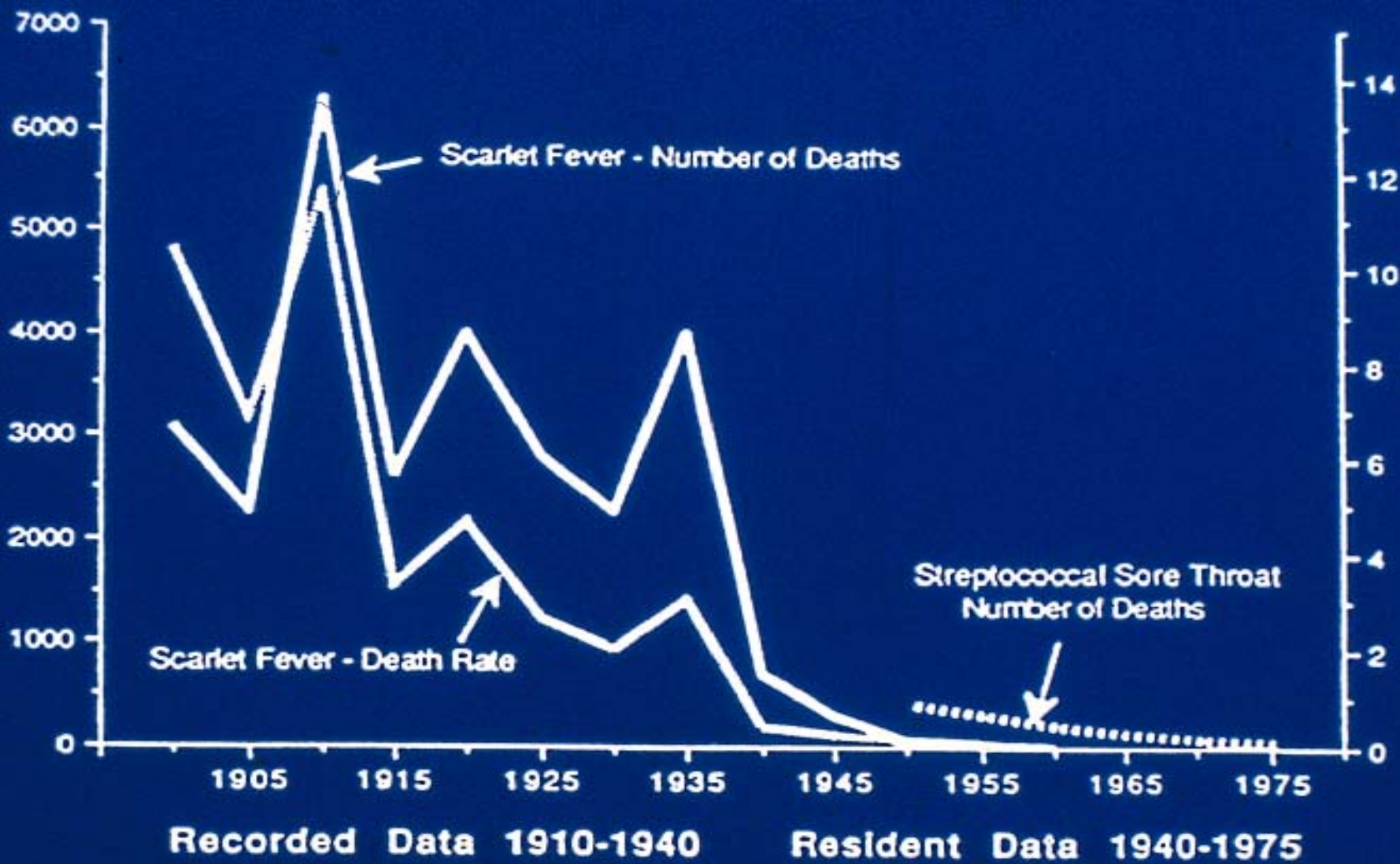


**New Approaches to Managing
Streptococcal Necrotizing Fasciitis:
Challenging the Dogma**

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ray, BM. Streptococcal infections. IN: Evans, AS, Bachman, PS, eds. Bacterial infections of humans. Epidemiology and control. New York: Plenum Medical

Invasive GAS Disease

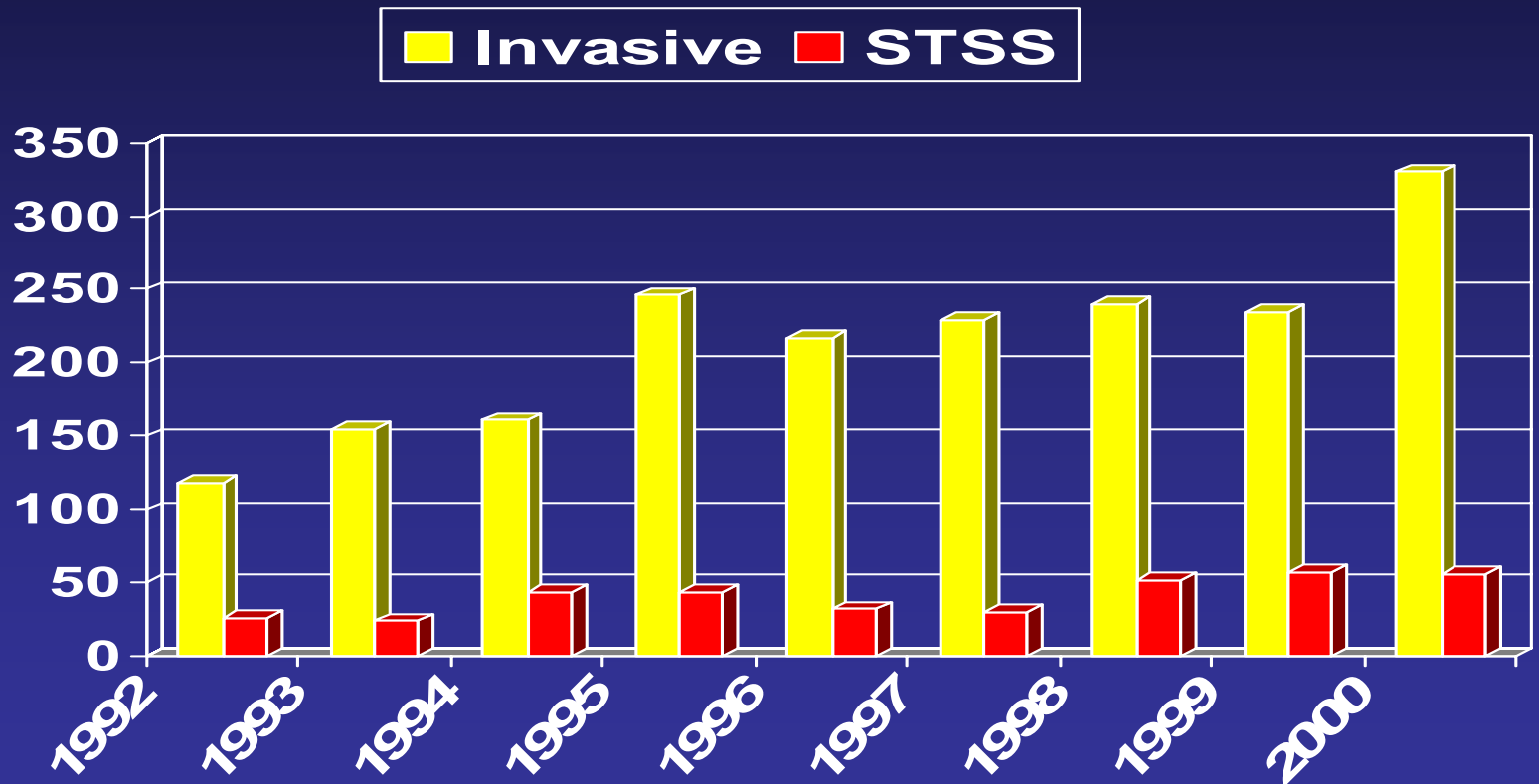
- Since 1980's
 - Increased incidence of disease
 - Recognition of STSS
 - Resurgence of necrotizing fasciitis
- Both M3 and streptococcal pyrogenic toxin A have been associated with more severe disease

Ontario GAS Study

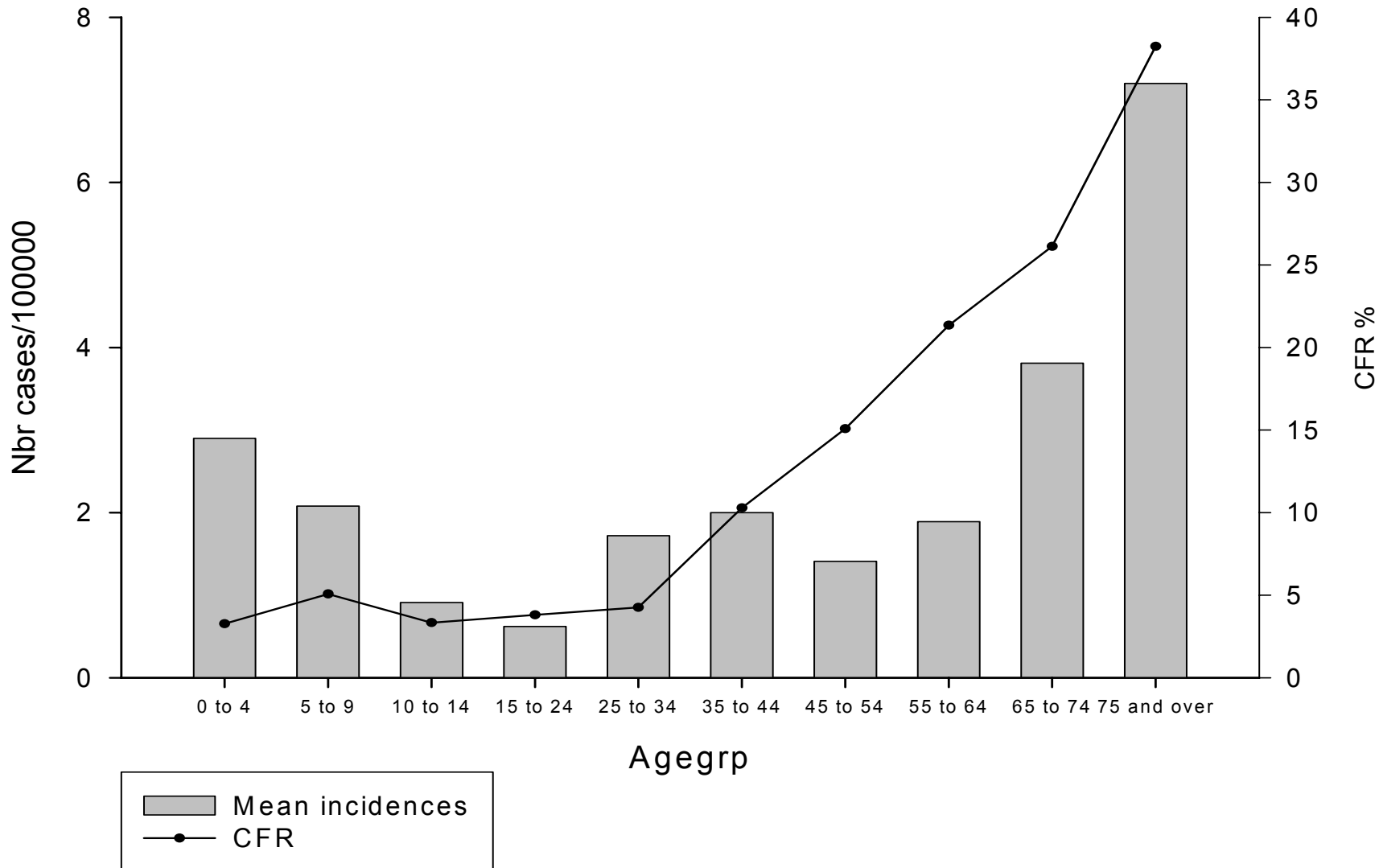
*Population-based surveillance for GAS since
1992-2000*

- Microbiology labs report sterile site isolates
- Physicians/ICPs provide clinical information

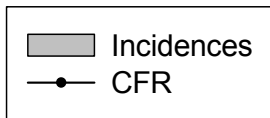
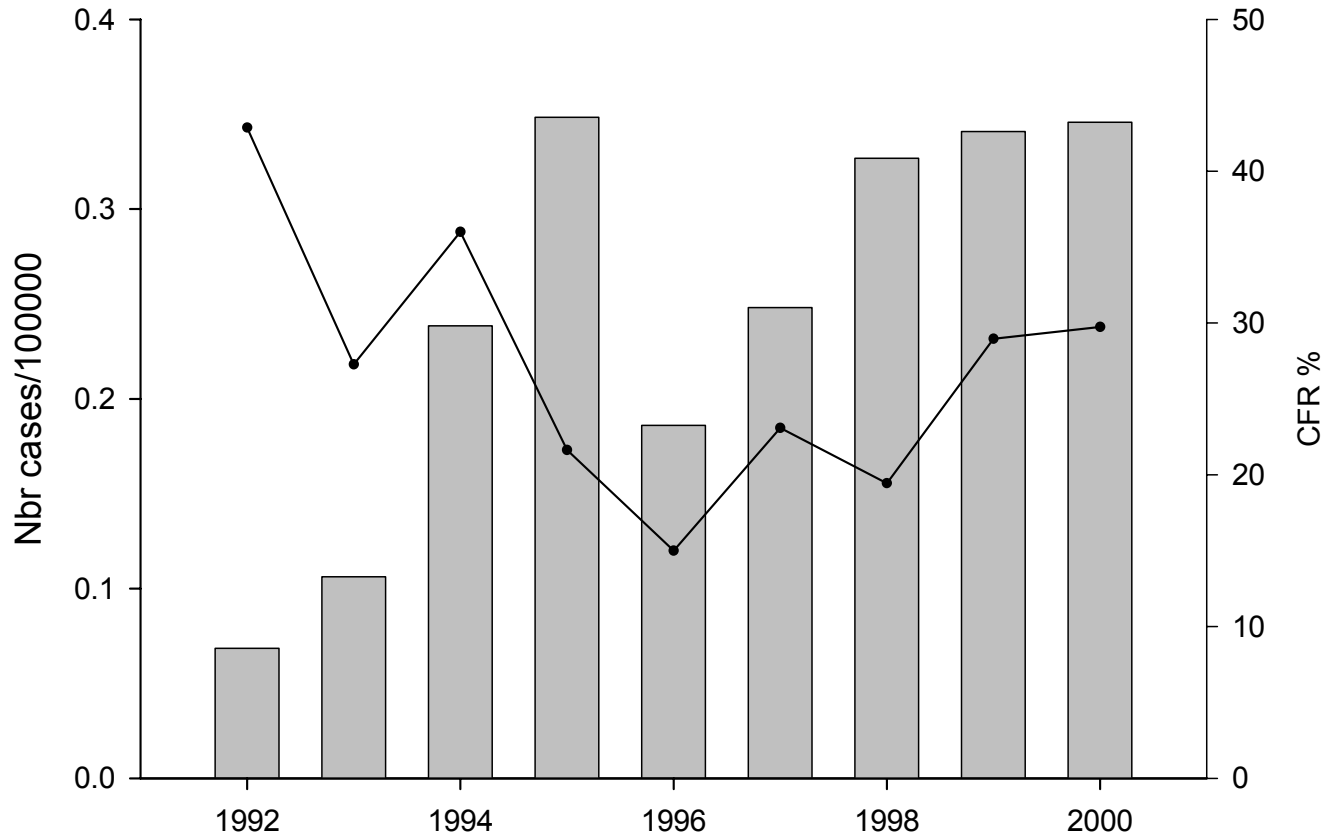
Invasive Group A Streptococcal Infections Ontario, Canada Jan 92 - Dec 00

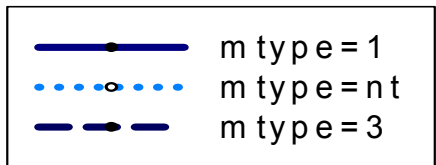
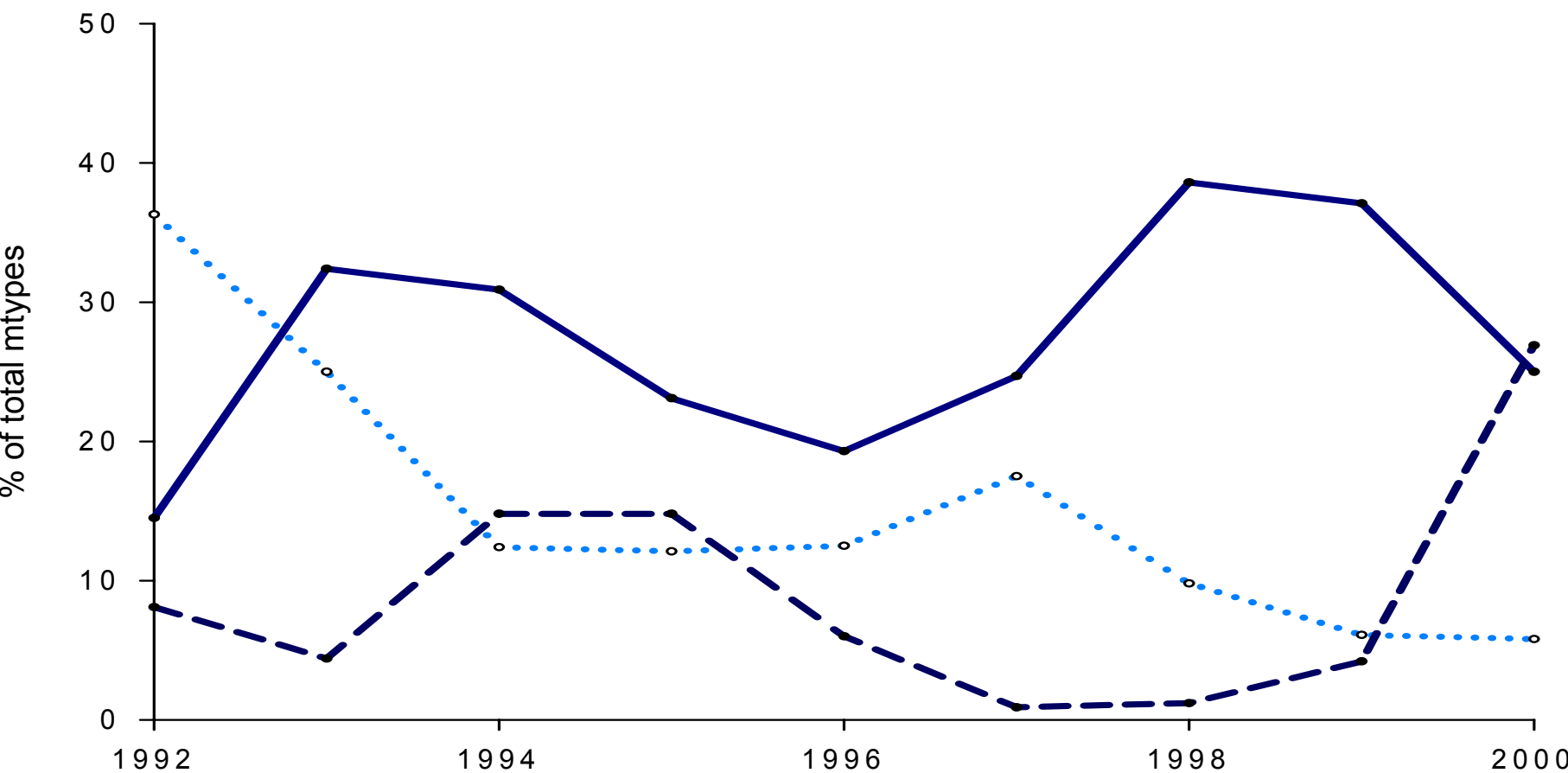


Mean incidences CFR by age groups Ontario



Incidences CFR NF Ontario





Outcome of patients with GAS infections

Syndrome	Mortality	
	Including STSS	Without STSS
All invasive GAS	15%	6%
CAP	38%	20%
Necrotizing fasciitis	26%	6%

ul R, et al. Am J Med, 1997, Davies D, et al. NEJM, 1996, Sharkawy A, et al. CID, 2002.

iller M et al. Arch Intern Med, 2003.

Medical Therapeutic Strategies

Intravenous immunoglobulin (IVIg)

- Antigen-specific effects
 - M proteins
 - Superantigens
- Anti-inflammatory effects

IVIG as Adjunctive Therapy in Toxic Shock

Several case reports of IVIG therapy of TSS

IVIG therapy in STSS:

- Case-control study (Kaul R, et al. 1999 Clin Inf Dis)**
- Multicenter placebo-controlled trial (Darenberg J, et al. 2003 Clin Inf Dis)**

Observational cohort study of IVIG therapy in STSS: Study Protocol

- *Study period:* 12/94 - 5/96
- *Recommendations:*
 - IVIG 0.4 g/kg/day, 1-4 days
 - Clindamycin, Penicillin
 - Surgical debridement if necessary
- **Consent for pre/post IVIG & convalescent blood**

Kaul R, et al. 1999 Clin Infect Dis 28:800.

Observational cohort study of IVIG therapy in STSS

Cases: STSS patients who received IVIG therapy within the study period, and were enrolled in Canada

Controls: STSS patients identified through active surveillance in Ontario 1/92 - 5/95

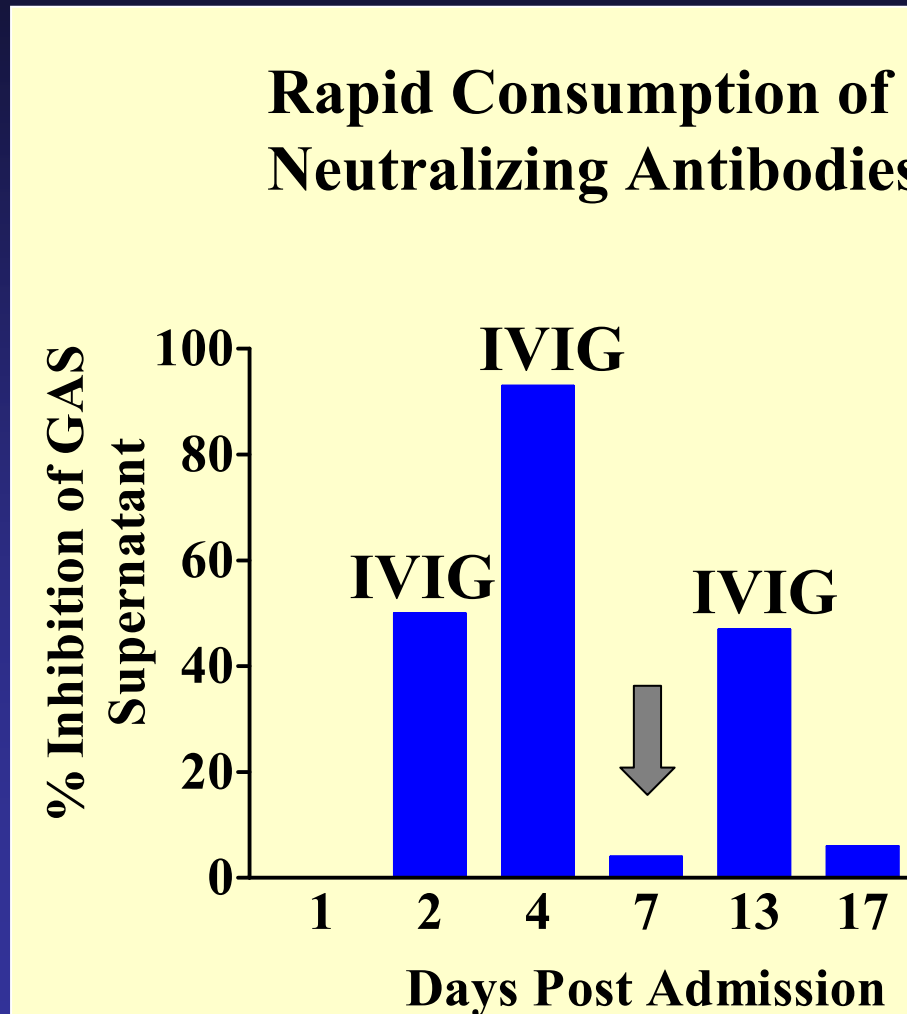
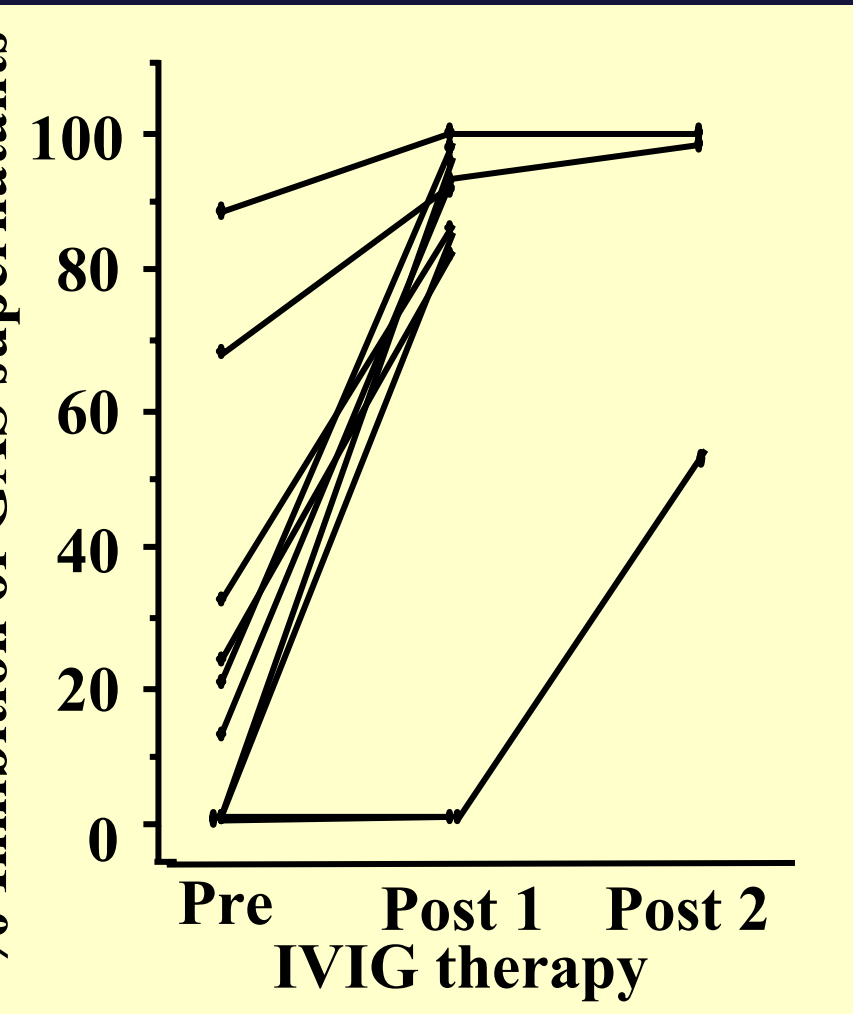
Inclusion criteria:

- effective antimicrobials
- survival >12h post STSS

Clinical Efficacy of IVIG

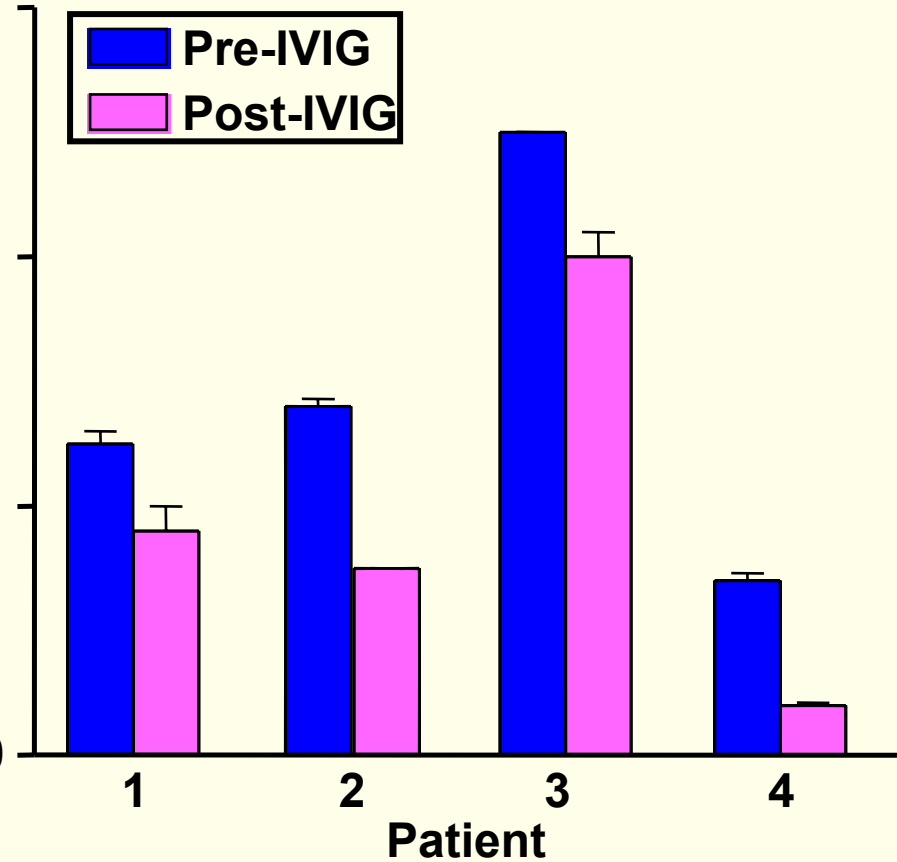
Survival (%)	Cases (n=21)	Controls (n=32)	<i>P</i> value
7 days	19 (90)	16 (50)	.01
30 days	14 (67)	11 (34)	.02

Plasma from Patients Post-IVIG Therapy Inhibits Mitogenic Activity Produced by their GAS Isolates

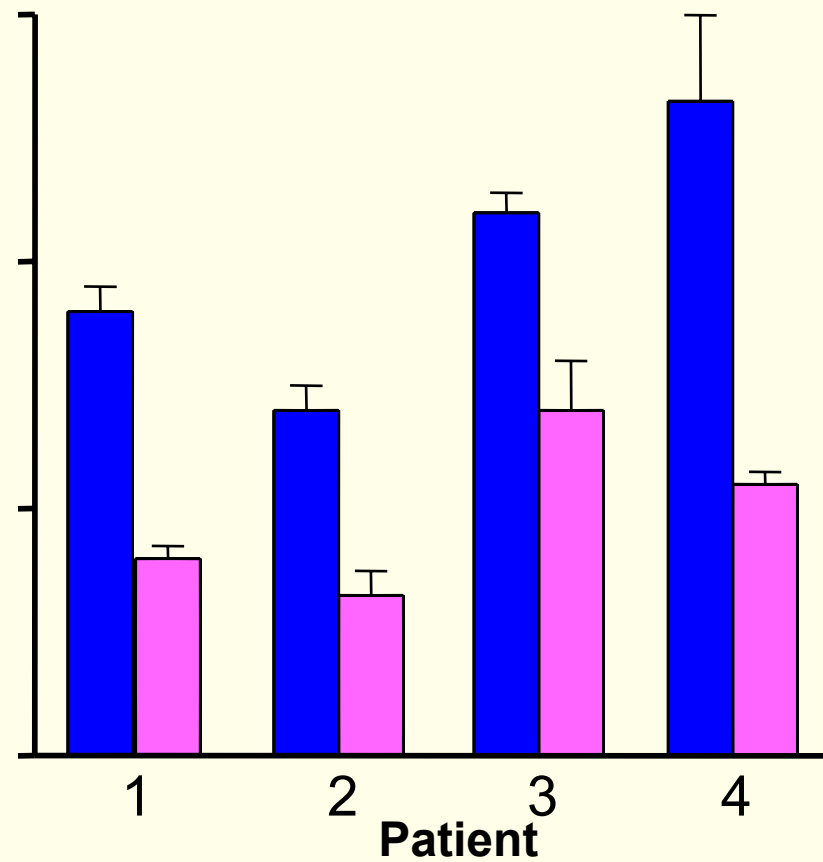


Cytokine Production in Circulation Pre- and Post-IVIG Therapy

TNF α -Production



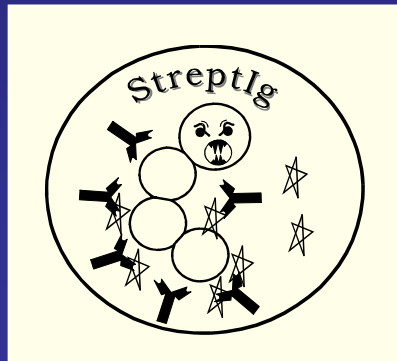
IL6-Production



Case-control Study

Provides strong support for the use of IVIG in STSS.

StreptIg-001: European Randomized, Double-blind Placebo Controlled Trial of IVIg in Streptococcal Toxic Shock Syndrome (STSS)



Darenberg J., et al. Clin Infect Dis 2003

StreptIg-001 study

01 Jan. 1999 - 16 May 2001

- 17 initiated centres:
 - 11 Sweden
 - 4 Norway
 - 1 Finland
 - 1 Netherlands
- Study terminated prematurely the 16 of May 2001 due to too slow patient recruitment, and problems with availability of IVIG

Study Protocol StreptIg-001

Inclusion criteria: STSS
≥18 years of age
Informed consent

Exclusion criteria:
Known hypersensitivity to IVIg
Underlying disease expected to cause death in 3 months

Study drugs:
Endobulin S/D, 1.0 g/kg day 1, 0.5 g/kg days 2 & 3
Albumin (1%), equivalent volume as IVIG in 3 days

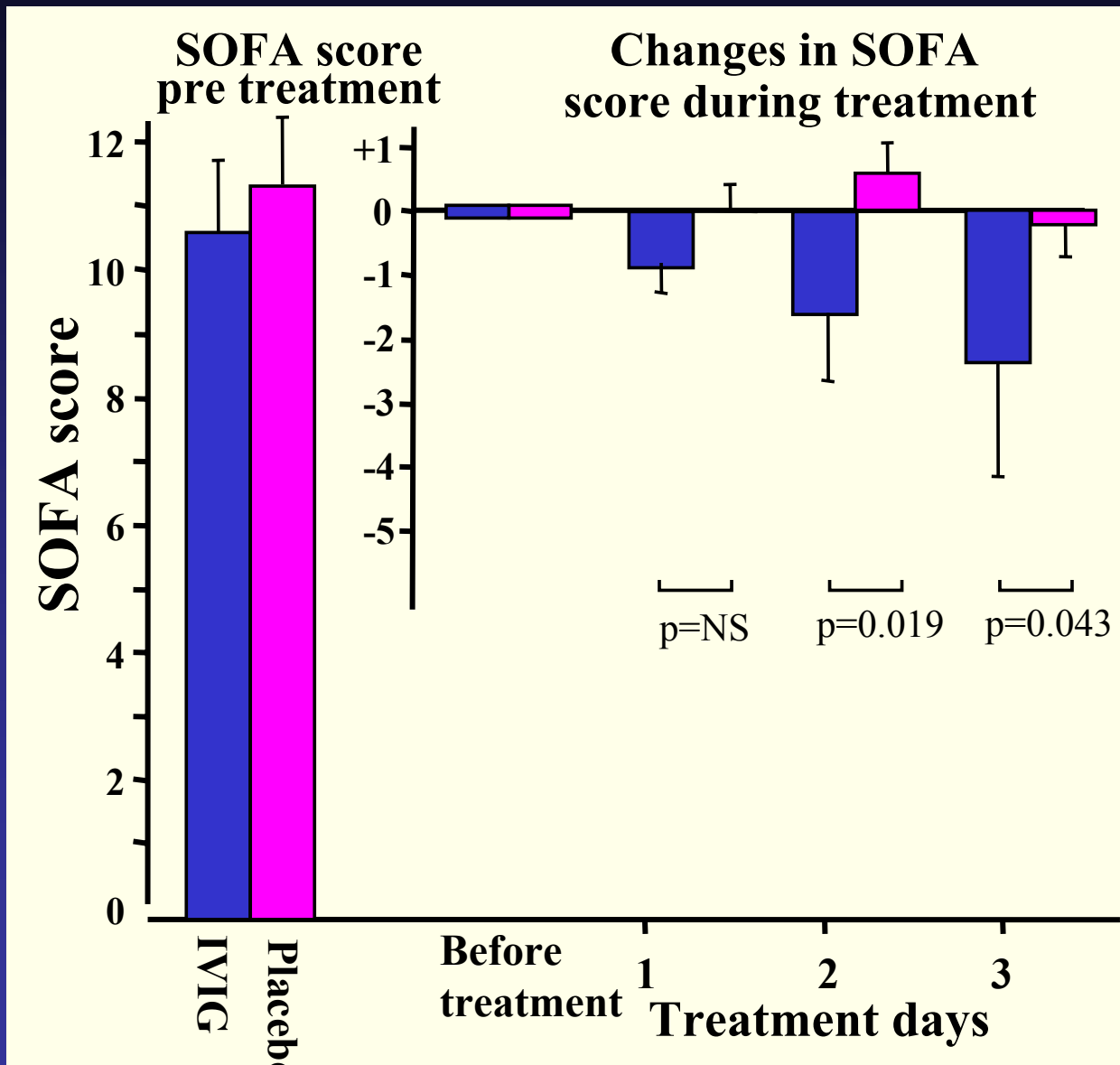
Antibiotic therapy:
i.v. clindamycin in combination with benzylpenicillin

Design: Total 120 patients, 2 interim analyses

Primary and Secondary Endpoints of StreptIg-001

Endpoint	IVIg (n=10)	Placebo (n=11)
Primary		
Mortality day 28, No. (%)	1 (10)	4 (36)
Secondary		
Time (h) to resolution of shock, median (range)	96 (2 - 159)	108 (47 - 294)
Time (h) to no further progression of NF/cellulitis, median (range)	20 (2 - 168)	24 (19 - 72)
Mortality day 180, No. (%)	2 (20)	4 (36)

Improvement in Organ Dysfunction Post-IVI



StreptIg-001 study

Trend to reduced mortality

Significant decrease in SOFA score post-IVIG administration

Surgical Approach to Severe GAS Soft Tissue Infections

Can we challenge the dogma?

Mandell's

- “In patients in whom the diagnosis is clearly suspected on clinical grounds-direct operative intervention is indicated”
- “Extensive incisions should be made through the skin and subcutaneous tissues and go beyond the area of involvement until normal fascia is found.”

Scientific Principles and Practise

- “...early recognition in conjunction with prompt, aggressive and extensive debridement.”
- “The clearest guidelines to determine the limits of resection involve removal of clearly infected necrotic tissue so that margins several centimeters into grossly normal healthy tissue are achieved”

Common Message

- If at all suspicious, early surgical exploration essential
- If find necrotic tissue, wide debridement, to and including healthy margin, is life saving

Proponents for early surgical intervention

- Stamenkovic I, Lew PD, NEJM. 1984;310:1689-93
- Pessa ME, Howard RJ, Surg Gyn & Obst. 1985;161:357-6
- Freischlag JA, et al. Amer J Surg. 1985;149:751-755
- Sudarsky LA, et al. Ann Surg. 1987;206:661-5
- Chelsom J, et al. Lancet. 1994;344:1111-15
- McHenry CR, et al. Ann Surg. 1995;221:558-65
- Mohammedi I, et al. Inten Care Med. 1999;25:829-34

Characteristics of studies

- All retrospective
- Multiple etiologies
- Patients gathered from 2 to 24 years

Surgery in infections

- Goals of surgery
 - Reduce bacterial load
 - Abscess drainage (antibiotics limited effect)
 - Eradicate the source of infection?
 - Remove devitalized tissue
- Timing
 - Early versus late

Successful management of severe GAS soft tissue infections using an aggressive medical regimen including intravenous polyspecific immunoglobulin together with a conservative surgical approach

- 7 patients with severe soft tissue infection caused by GAS, who all were treated with effective antimicrobials and high-dose IVIG.
- Surgery was either not performed or only limited exploration was carried out.

Successful management of severe GAS soft tissue infections using an aggressive medical regimen including intravenous polyspecific immunoglobulin together with a conservative surgical approach

- All patients survived
- Immunostaining of tissue biopsies from 2 of the patients revealed high levels of GAS, superantigen and pro-inflammatory cytokines
- Follow-up in one patient 66 h post-IVIG administration revealed dramatically reduced superantigen and pro-inflammatory cytokines

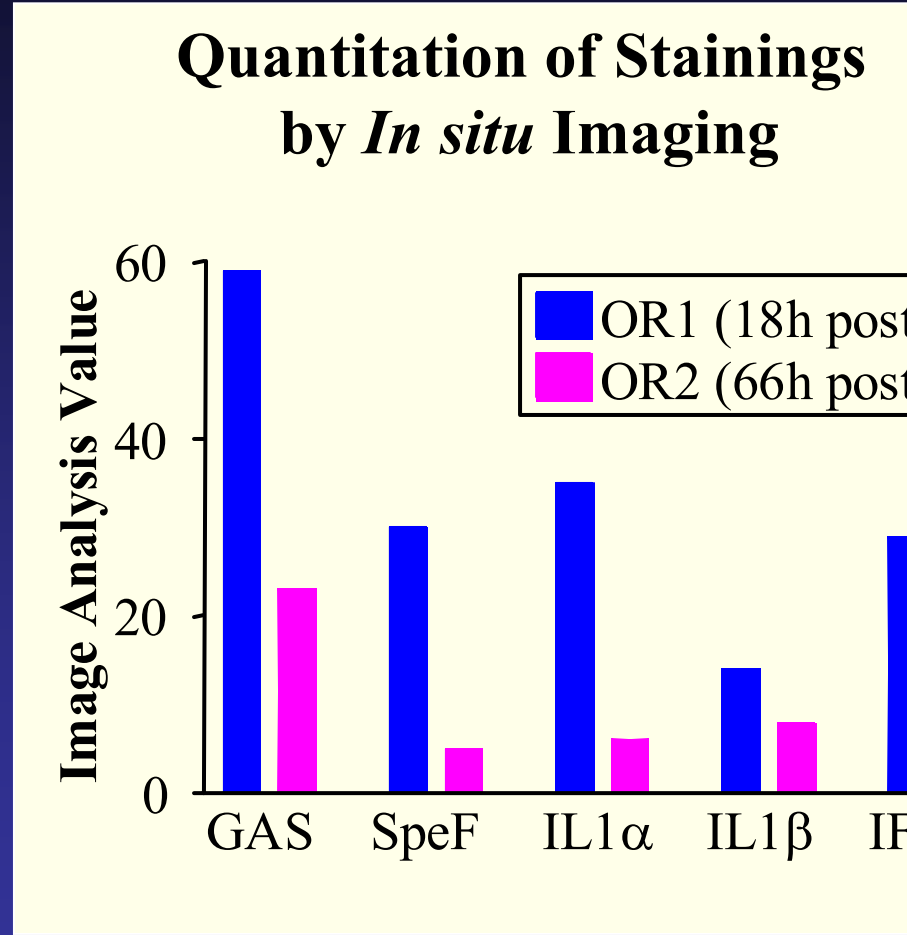
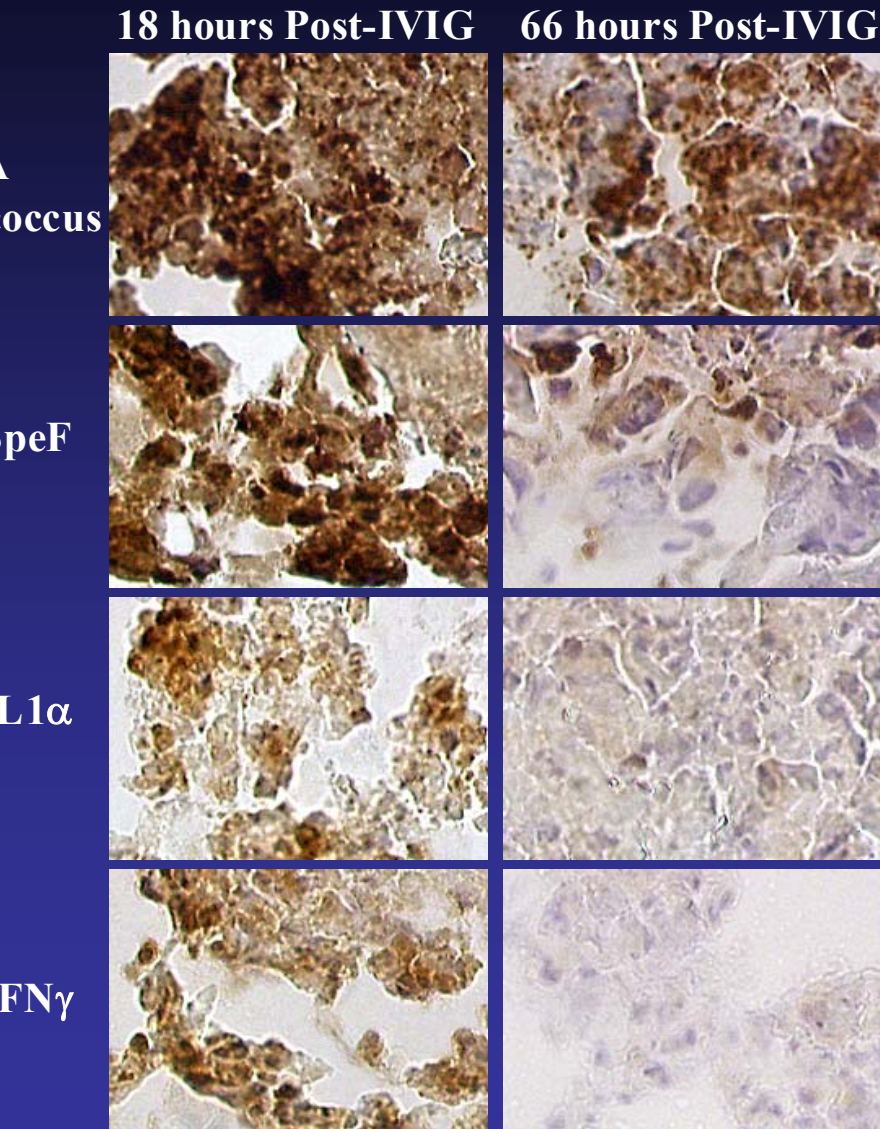




Tissue Pre and Post IVIG

- Bacterial load, superantigen expression and cytokine levels in tissue biopsies
- The stainings were quantified by acquired computerized image analysis, and the results are presented as percent positively stained area times mean intensity of positive staining.

Plastic Reduction in Bacterial Load and Inflammation Post-IVIG at the Local Site of Infections





Final Case

- a 38 YO otherwise healthy woman, started to experience an increasingly severe sharp right shoulder and arm pain during the day
- blood pressure was 85/60 mm Hg
- coagulation times were abnormal
- CT exhibited extensive soft tissue, muscle and fascial swelling of her right arm, right chest wall, and right flank extending to her iliac crest





1815

- she had local superficial exploration of upper arm
- pathology showed necrotic skin and fat
- post-op she developed ARDS
- discharged from hospital on day 12

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