SEVERE STREPTOCOCCAL INFECTION

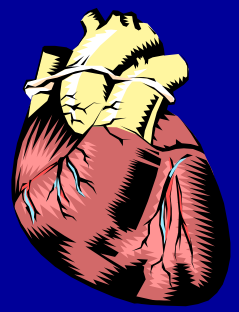
‘AN OLD BUT ACTIVE ENEMY’

Dr Graham Douglas

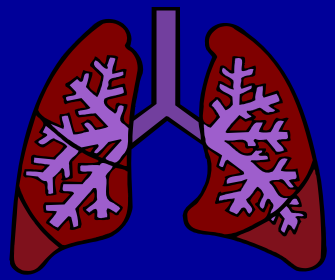
Aberdeen Royal Infirmary

TOP 3 CAUSES OF DEATH IN THE UK

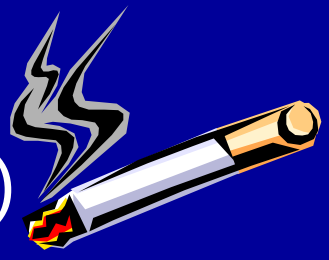
1 Ischaemic Heart Disease
(101,000 deaths & falling)



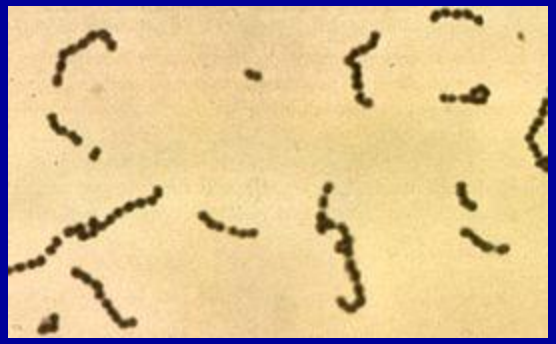
2 Sepsis/Pneumonia
(33,000 deaths & rising)



3 Lung Cancer
(29,000 deaths & rising in women)



STREPTOCOCCI



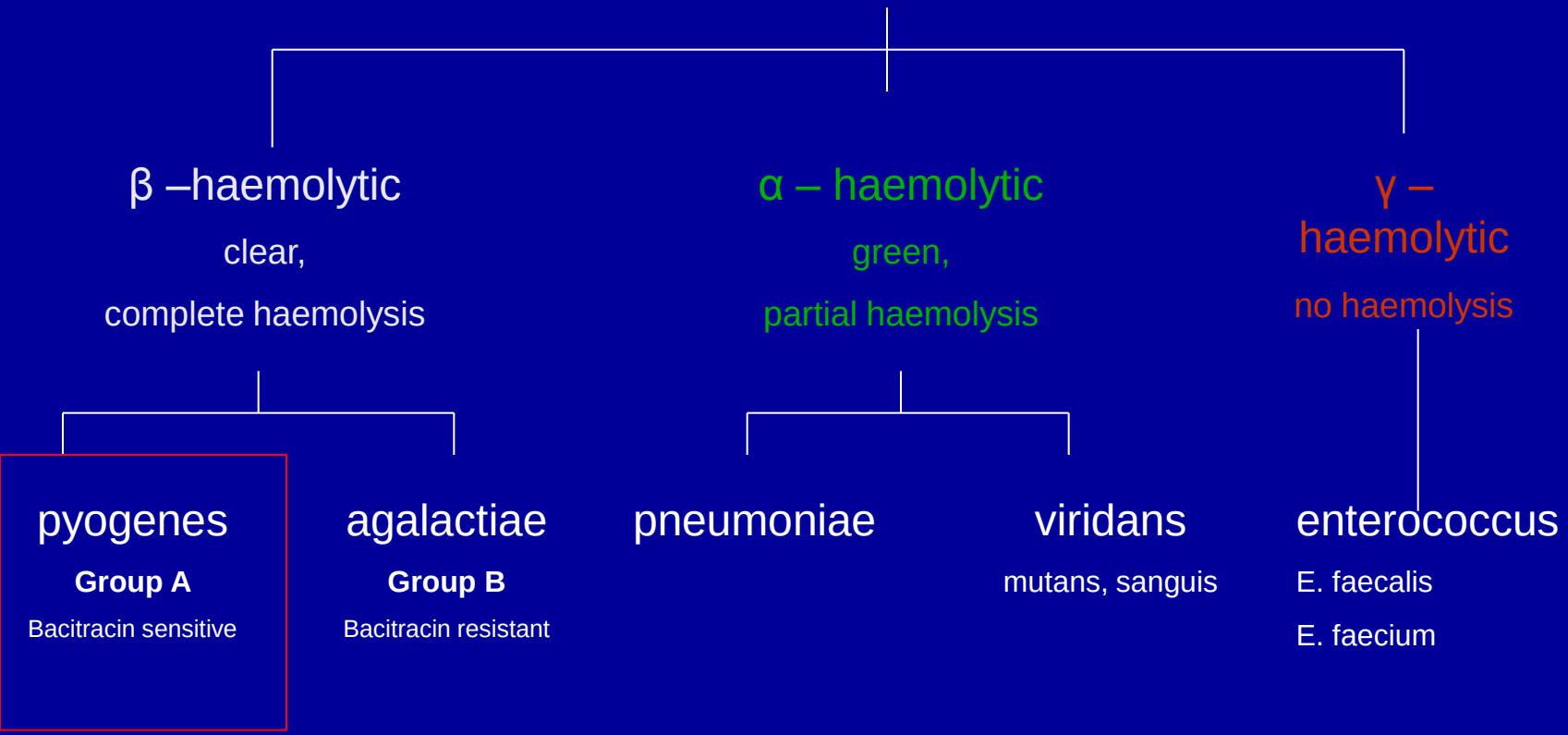
- Spherical Gram – positive bacteria
- Cellular division occurs along a single axis – so grow in chains or pairs. (Streptos – Greek meaning ‘twisted chain’)
- In contrast Staphylococci divide along multiple axes so appear in ‘grape-like’ clusters.

PATHOGENIC SPECIES

- S. agalactiae
- S. anginosus
- S. bovis
- S. canis
- S. equi
- S. iniae
- S. mitis
- S. mutans
- S. oralis
- S. parasanguinis
- S. perosis
- S. pneumoniae
- S. pyogenes
- S. ratti
- S. salivarius
- S. salivarius ssp. thermophilus
- S. sanguinis
- S. sobrinus
- S. suis
- S. uberis
- S. vestibularis
- S. viridans

22 species described

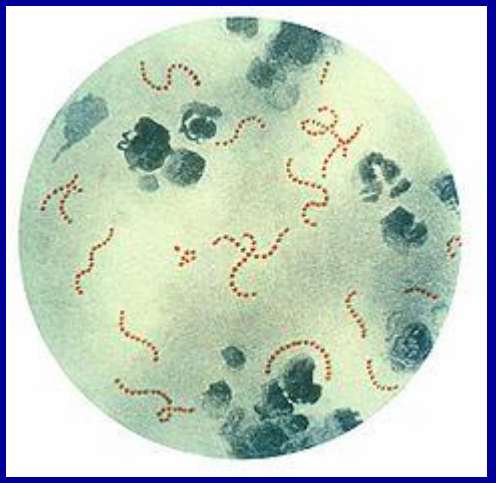
STREPTOCOCCUS



Classification of *streptococcus*

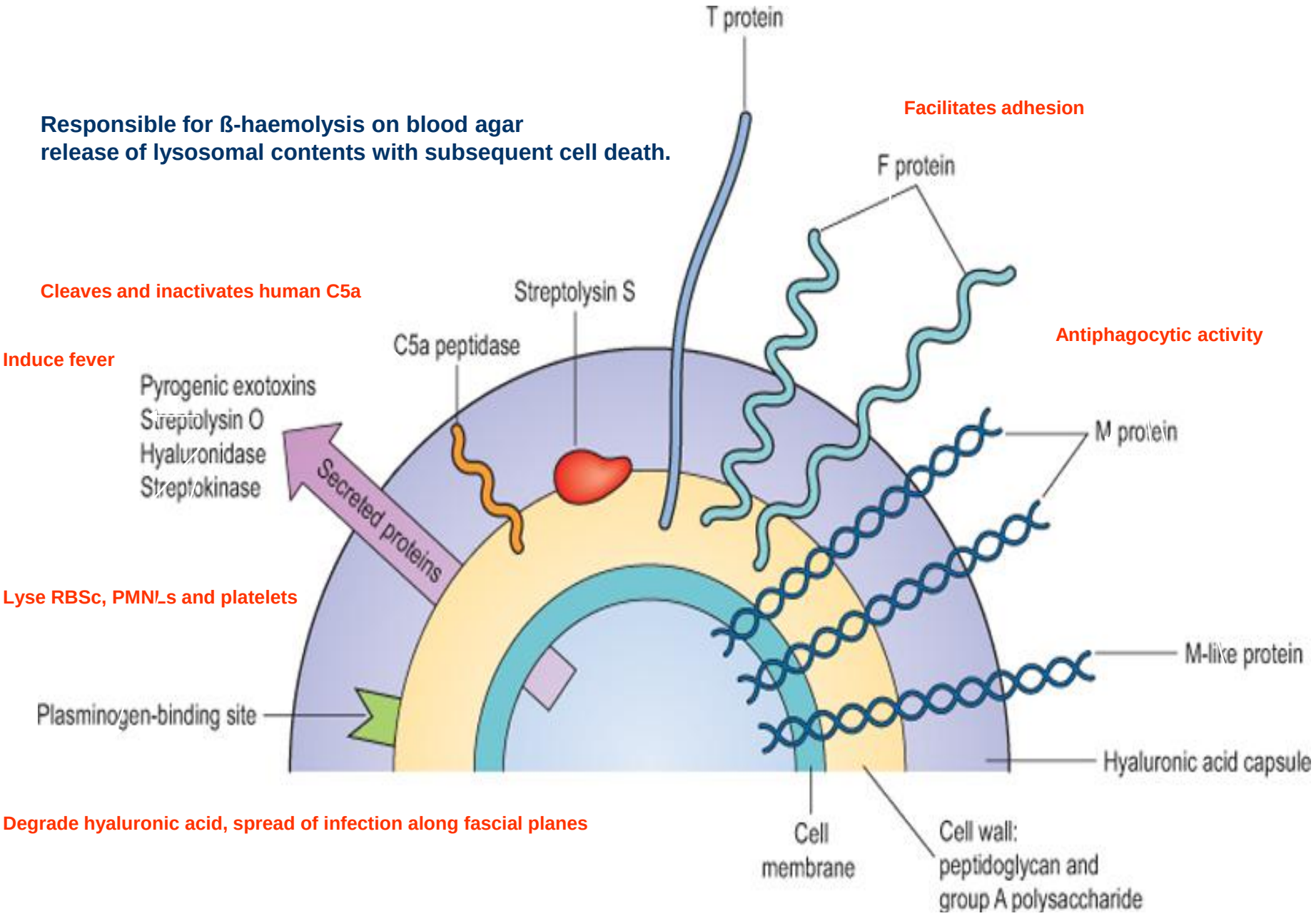
Streptococcus pyogenes is Group A beta-haemolytic

STREPTOCOCCUS PYOGENES



- Nowadays known as GROUP A STREPTOCOCCUS (GAS)
- Associated exclusively with human infection
- Only human reservoir is skin or mucous membranes
- Classified by Rebecca Lancefield, US Microbiologist in 1928 – based on its M. protein, surface virulence factor

Responsible for ß-haemolysis on blood agar
release of lysosomal contents with subsequent cell death.



Schematic diagram showing the location of virulence-associated products of *Str. pyogenes*

GROUP A STREPTOCOCCAL INFECTION

In the UK over the last 40 years:

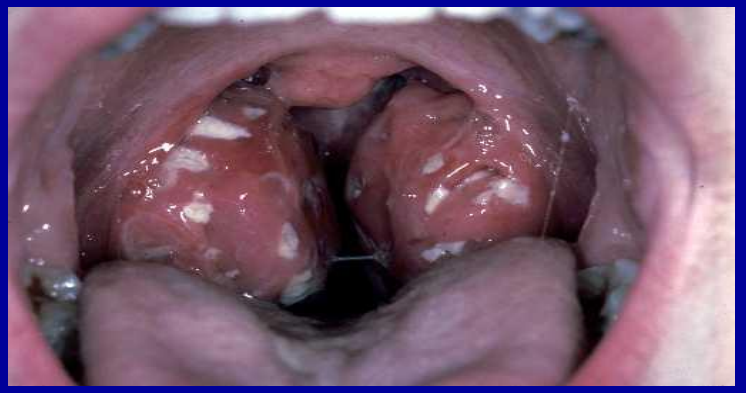
- Pharyngitis, erysipelas & scarlet fever have become milder
- Rheumatic fever & post-streptococcal glomerulonephritis rarer
- Invasive GAS infection commoner:

  1985-94 3 fold increase in GAS bacteraemia (US)

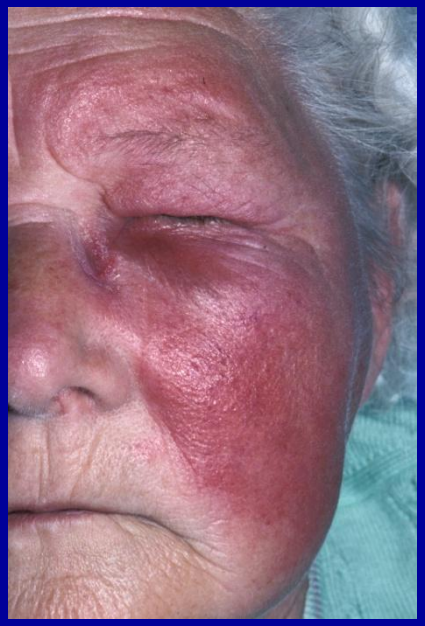
  6-8 fold increase in those 30-50 years

GROUP A STREPTOCOCCAL INFECTIONS

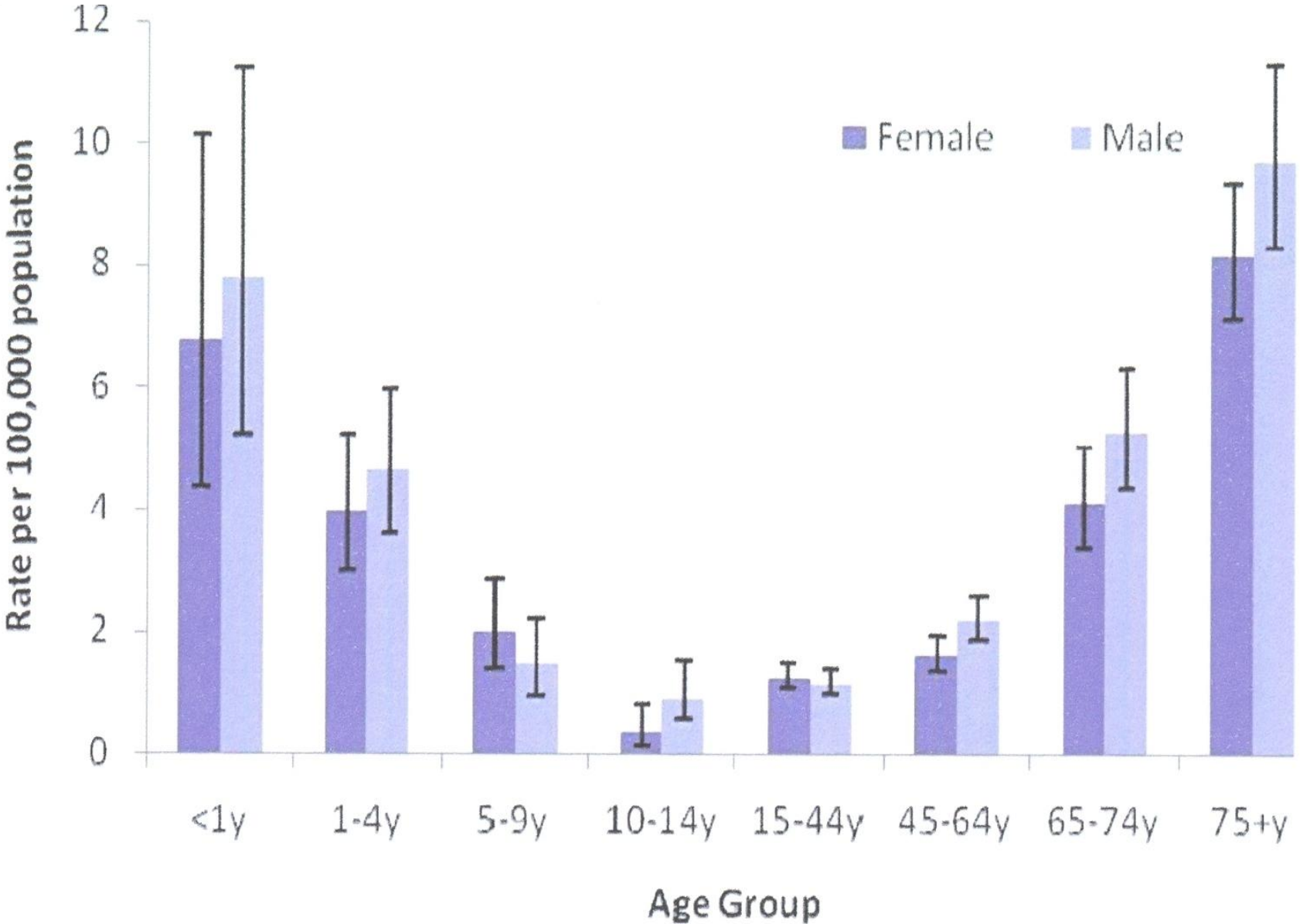
- NON-INVASIVE
  - Pharyngitis
  - Tonsillitis



Soft Tissue Infection
- Scarlet Fever
- Impetigo
- Erysipelas

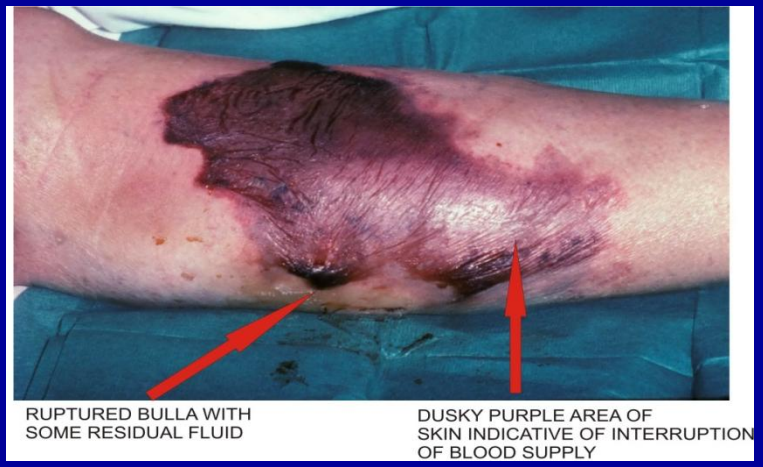


Age-specific rates of group A streptococcal bacteraemia reports: England, Wales and Northern Ireland 2009



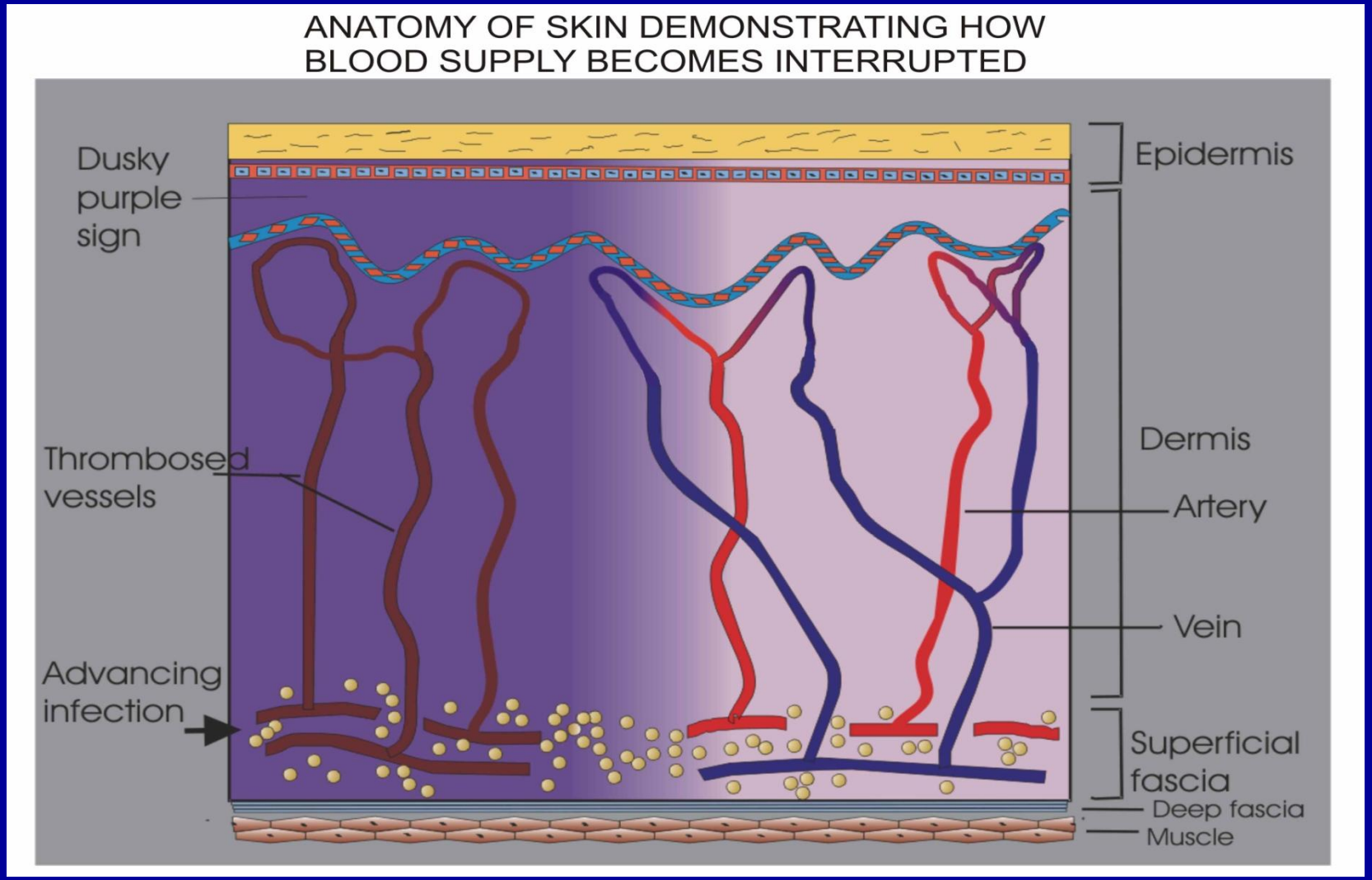
GROUP A STREPTOCOCCAL INFECTIONS

- INVASIVE
  - Bacteraemia
  - Pneumonia
  - Necrotizing fasciitis
  - Spontaneous gangrenous myositis



- Now 3.5/100,000/yr in UK, US & Australia

- 50% of GAS bacteraemia complicated by Toxic Shock Syndrome



- GAS infection occurs within 72 hrs at the site of minor trauma
  e.g. bruise, sprained muscle
- Presents with abrupt pain preceding physical findings

RISK FACTORS FOR INVASIVE GAS INFECTIONS

Patients of all ages – not just immunosuppressed

CHILDREN:

- Burns
- Malignancy
- Trauma
- Varicella

AGE 14-40 Years:

- Puerperal sepsis – re-emerging! (Semmelweis 1850s)
- IVDU – tends to be less severe
- HIV infection - ~40x increase

AGE > 40 Years:

- Burns
- Surgery esp. suction lipectomy, breast reconstruction, gynae procedures
- Non-penetrating trauma
- Diabetes mellitus
- Alcoholism
- Malignancy
- Corticosteroid therapy

(Hospital acquired GAS infection can also occur)

VARICELLA & INVASIVE GAS INFECTION

- In a study of 2500 US school children with varicella
  – 0.5% has GAS bacteraemia.

- Rate of varicella related GAS infection as a % of all invasive GAS infections has fallen in the US with vaccination:
  - Pre vaccine era (1993 – 1995) 27%
  - Widespread vaccine use (1999 – 2001) 2%

- Recent study from North Carolina:
  131 patients (60% were adults) with invasive GAS infection – 11% had varicella

Invasive Group A Streptococcal Infection Concurrent with 2009 H1N1 Influenza

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We describe 10 patients with 2009 H1N1 influenza and concurrent invasive group A streptococcal infection with marked associated morbidity and mortality. Seven patients required intensive care, 8 required mechanical ventilation, and 7 died. Five of the patients, including 4 of the fatalities, were previously healthy.

Since the emergence of the 2009 H1N1 influenza virus, conflicting reports have been published about the role of bacterial coinfection in the severity of disease. Although recent studies have found bacterial coinfection in 29%–43% of fatalities with 2009 H1N1 influenza, several case series of hospitalized patients have noted the infrequent detection of bacterial coinfection, ranging 2%–4% [1–4]. Infection with *Streptococcus pneumoniae* or *Staphylococcus aureus* concurrent with seasonal influenza has been associated with severe morbidity and mortality [5]. Descriptions of severe illness due to coinfection with *Streptococcus pyogenes* (group A *Streptococcus*) have been uncommon. In this report, we describe 10 patients coinfected with 2009 H1N1 influenza and invasive group A *Streptococcus* (GAS), with associated severe morbidity and mortality.

Methods. Confirmed and probable cases of 2009 H1N1 influenza were reported to the California Department of Public Health (CDPH) by local health departments. Testing for influenza is recommended for hospitalized patients and patients who die with influenza-like illness (defined as temperature >37.8°C plus cough and/or sore throat). Patients who have influenza-like illness and real-time polymerase chain reaction (PCR) test results that are confirmed 2009 H1N1 influenza are considered to be confirmed cases of 2009 H1N1 influenza, whereas patients with influenza-like illness and real-time PCR test results positive for influenza A but negative for human subtypes H1 and H3 are considered to be probable cases of 2009 H1N1 influenza. Through 11 August 2009, health department and hospital staff completed standardized case report forms for all hospitalized patients and fatalities. Subsequently, individual case reports were completed only for intensive care unit (ICU) patients and fatalities. Medical records were reviewed to verify bacterial infection and to determine clinical course. Infections were considered to be invasive if GAS was isolated from a sterile site. GAS *emm* typing and typing of the streptococcal inhibitor of complement (*sic*) gene were performed by the CDPH Microbial Diseases Laboratory [6, 7].

Results. During 3 April–26 December 2009, there were 8075 hospitalized patients and/or fatalities with 2009 H1N1 influenza reported in California, including 1656 ICU patients and 461 fatalities. Of these 8075 persons, 10 patients with concurrent invasive GAS infection were identified (Table 1). Two of these patients were part of a household cluster of influenza-like illness; a third household member had invasive GAS but had negative test results for influenza.

The median age of the 10 patients with 2009 H1N1 influenza and invasive GAS infection was 37 years (range, 5–66 years); 3 were <18 years old. Six patients (60%) were male; 7 (70%) were Hispanic. The most common symptoms before admission were fever (in 10 [100%]), cough (in 8 [80%]), nausea or vomiting (in 7 [70%]), shortness of breath (in 7 [70%]), sore throat (in 5 [50%]), diarrhea (in 5 [50%]), and muscle aches (in 5 [50%]). None of the patients with sore throat had exudative pharyngitis. No patients had skin or soft-tissue infection. The median time from onset to hospital admission was 6 days (range, 4–14 days). All 9 patients who had chest radiographs performed had evidence of pneumonia. Seven patients required ICU support and mechanical ventilation. There were 7 fatalities; 4 of the fatalities occurred <24 hours after presentation at the hospital, including a patient who presented in full cardiac arrest. The median length of hospitalization for the 6 patients hospitalized ≥24 hours was 15 days (range, 1–71 days).

Five of the 10 patients were previously healthy, including 4 of the fatalities. Underlying medical conditions for the re-

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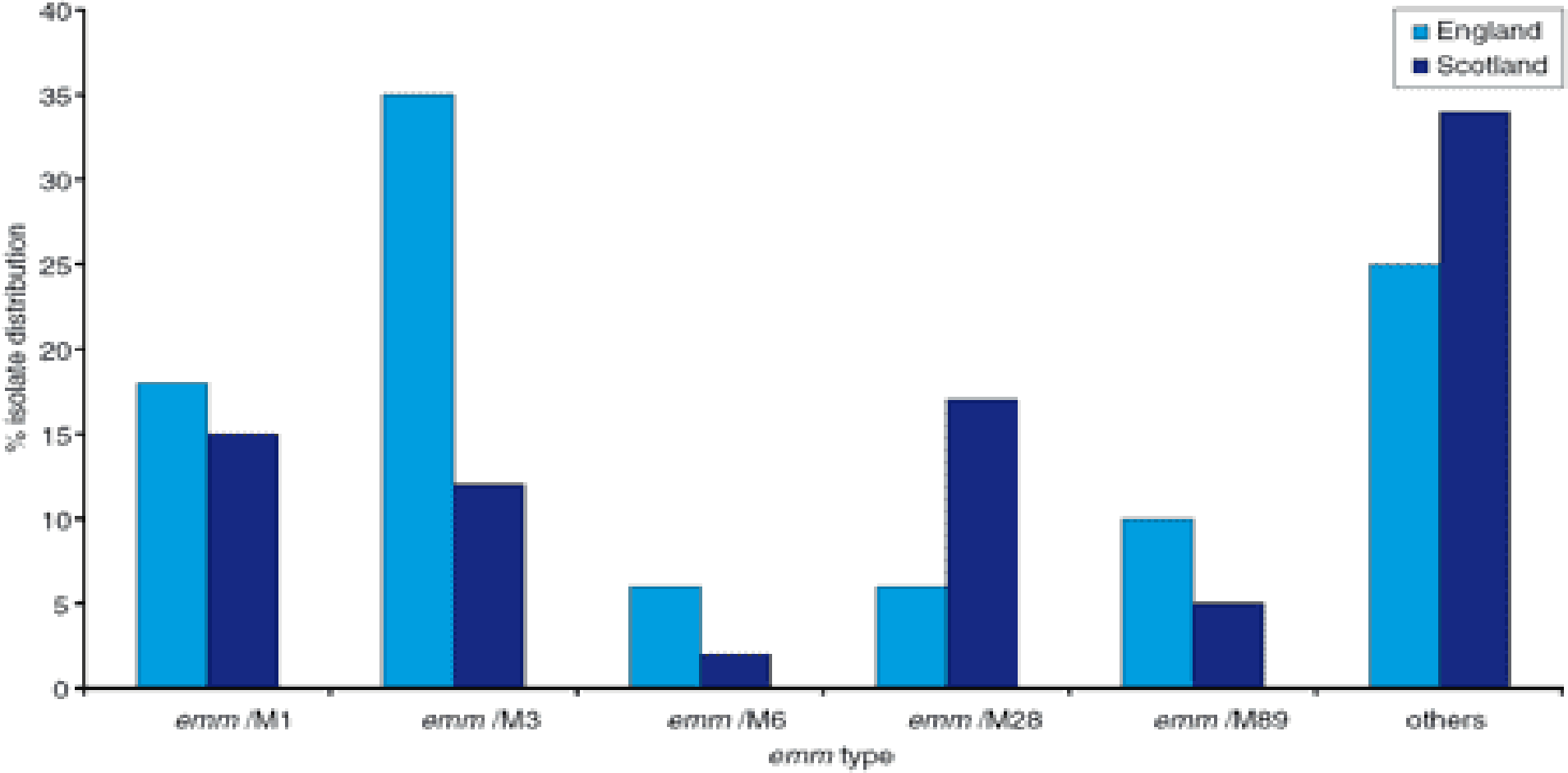
- Strept. Pyogenes pneumonia was found during the 1918 H1N1 pandemic
- ? GAS pneumonia associated with recent H1N1 (2009) “Swine Flu” pandemic

emm type distribution of invasive group A streptococcal isolates from England and Scotland: 1 January – 31 March 2009



Emm/M3 particularly associated with more severe invasive GAS infection.

GAS TOXIC SHOCK SYNDROME

- Consider in any patient presenting from the community with shock
  - esp. if there is a recent history of trauma, severe pain or fever

- Main Criteria: US Working Group on Severe Streptococcal Infection
  1. Isolation of GAS from a normally sterile site
     - e.g. blood, CSF, pleural or peritoneal fluid, tissue biopsy or wound.
  2. Hypotension (systolic < 90mmHg)

Plus 2 or more of:

- Renal impairment (creatinine >200mg/l)
- Coagulopathy (thrombocytopenia, DIC)
- Liver involvement (ALT x 2 upper limit)
- ARDS on Chest Xray
- Erythematous rash
- Soft tissue necrosis (necrotizing fasciitis, myositis, gangrene)

CLINICAL FEATURES OF GAS TOXIC SHOCK SYNDROME

Mediated by toxins (superantigens) stimulating T cell responses and releasing large quantities of cytokines (IL1, TNF alpha, IL6 & IFN gamma)

- Prominent pain often precedes physical signs
- Ecchymoses, sloughing of the skin progressing to necrotizing fasciitis/myositis
- Hypotension and fever

- About 20% do not have soft tissue infection

  Endophthalmitis

  Peritonitis

  Postpartum Sepsis

  Myocarditis

  Pneumonia

MANAGEMENT OF GAS TOXIC SHOCK SYNDROME

Multidisciplinary approach: surgeons, infection specialists & intensivists

- Haemodynamic support
  (intractable hypotension & diffuse capillary leak)
  - massive amounts of fluid (>10 litres/day)
  +
  - inotropic support

- Surgical therapy – prompt and aggressive exploration and debridement of suspected deep – seated GAS infection.

- Antibiotic therapy

ANTIBIOTIC THERAPY FOR SEVERE GAS INFECTION

- S. pyogenes remains exquisitely sensitive to penicillin *in vitro*
- But for invasive GAS infection, mortality higher if penicillin used alone
- Why?

Penicillin -

- Most effective against rapidly growing bacteria
- Severe deep-seated GAS infection produce very high concentration of organisms
- Less penicillin – binding protein during stationary phase

ANTIBIOTIC THERAPY FOR SEVERE GAS INFECTION

- CARBAPENEM e.g. Meropenem 1 gm every 8hrs IV

  or

- PENICILLIN + BETA-LACTAMASE INHIBITOR e.g. Piperacillin/Tazobactam 4.5gm every 6 hrs IV

Plus CLINDAMYCIN 900mg every 8hrs IV

- Clindamycin – Not affected by inoculum size or stage of growth
  Suppresses synthesis of bacterial toxins
  Inhibits the anti-phagocytic M protein
  Suppresses TNF production

- DURATION OF THERAPY – At least 14 days

ADJUNCTIVE THERAPY FOR SEVERE GAS INFECTION

- Hyperbaric oxygen – reported benefit in small number
- Anti TNF therapy – some success in baboon studies
  – no human clinical trials
- Intravenous immune globulin (IVIG)

IV IMMUNE GLOBULIN IN SEVERE GAS INFECTION

- IVIG – neutralises streptococcal toxins
  – inhibits T-cell proliferation
  – inhibits TNF-alpha & IL-6

- RCT of 21 patients with GAS toxic shock syndrome.
  IVIG 1g/kg day 1; 0.5g/kg days 2 & 3 – or placebo
  All received IV Clindamycin & penicillin for 14 days
  Mortality 4 of 11 (36%) placebo group
  1 of 10 (10%) active IVIG group
  Clin Infect Dis 2003; 27: 333 – 340.

- Retrospective study of 192 children with streptococcal toxic shock syndrome
  not randomised (84 v 108)
  No differences in mortality or length of hospital stay
  Clin Infect Dis 2009; 49: 1369 - 76

PROGNOSIS OF SEVERE GAS INFECTION

- Mortality very variable (25 - 48%)
  - lower in children (18%)

Retrospective study of 66 patients in Japan (30 died)

- Worse prognosis with:
  - Lower WCC - < 1000 cells/m^3
  - Lower platelet count < 120,000
  - Higher serum creatinine
  - Lower body temperature
  - Lower systolic BP - < 99mmHg

SEVERE STREPTOCOCCAL INFECTION
SUMMARY

1. Non-invasive infection most common in very young and elderly – but severe GAS infection affects all ages and most not immunosuppressed

2. Invasive GAS infection often associated with Toxic Shock Syndrome

3. Pain preceding signs of soft tissue injury is common

4. Management should be multidisciplinary including early haemodynamic support and surgical debridement (if appropriate)

5. IV Clindamycin with a penicillin for at least 14 days is the treatment of choice

6. IV immune globulin therapy may have a role

NOTEABLE PEOPLE AFFLICTED BY GAS INFECTION/ NECROTISING FASCIITIS

- **King Herod, the Great of Judea** – may have died of Fournier's gangrene (necrotising fasciitis of the groin & genitalia)
- **Lucien Bouchard** – former Premier of Canada – lost his leg in 1994
- **Melvin Franklin** – bass singer with The Temptations – survived without amputation of his arm 1995
- **Eric Allin Cornell** – winner of 2001 Nobel Prize for Physics – lost his left arm and shoulder 2004
- **Jan Peter Balkenede** – former Prime Minister of the Netherlands - almost lost a leg in 2004
- **David Walton** – member of Bank of England's Monetary Policy Committee - died 2006
- **Alan Coren** – writer and satarist & former Rector of St Andrew's University - survived in 2006