



# SAHLGRENKA ACADEMY

## **Invasive group A Streptococcus infections in Gothenburg, Sahlgrenska University Hospital, January 2008 – June 2013**

Degree Project in Medicine

Louice Sehlberg

Programme in Medicine

Gothenburg, Sweden 2016

Supervisor: Lars Hagberg

Institution of Biomedicine, Department of Infectious Diseases

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## **ABSTRACT**

**Background:** Invasive group A Streptococcal infection (iGAS) is a severe disease, often requiring admission to an Intensive Care Unit (ICU). Incidence of iGAS in Sweden has markedly increased during the last 30 years. The reason for this is not fully understood.

**Aim:** First, to do a survey on local epidemiology, clinical manifestations and treatment for iGAS. Second, to investigate whether CRP and S-lactate can be used as early predictors for intensive care and death, and if there is a correlation between CRP and S-lactate.

**Method:** A retrospective medical record review of adults treated for iGAS at Sahlgrenska University Hospital, Gothenburg between 1<sup>st</sup> January 2008 and 30<sup>th</sup> of June 2013. Descriptive analysis was used for the first aim. For the second we used Fisher's Exact Test for S-lactate, and visualization with boxplot for CRP, as predictive values for ICU and death. Pearson's analysis for correlation was performed correlation between CRP and S-lactate.

**Results:** 146 patients (60 female, 86 male, median age 61 years) were identified from medical records. Local incidence followed the same trend as the national. Incidence was highest in November - May. The main verified underlying focuses were skin and soft tissue (48%) and lung (14%). Throat was suspected in only 4 %, and in 14% of the patients focus remained unknown. Antibiotics were given both as mono therapy and combined therapy. The most common antibiotic treatment before culture was cephalosporins or Penicillin G often combined with aminoglycosides. After etiological diagnosis was confirmed, the most used antibiotics were Penicillin G, Penicillin V and clindamycin. Twentyeight % of the patients (n=41, median age 55 y.) was admitted to ICU, and 49% (n=20) of those had no major comorbidity. Over all mortality rate within 1 month after hospital discharge was 12% (n=17/146, median age 79 y.). Four of those had no major comorbidity. The total number of patients with S-lactate sample taken was 102. Patients with initial S-lactate < 2.0 mmol/l were never admitted to ICU, however, 7% of them died.

S-lactate 2.0 - 3.9 mmol/l led to ICU in 39% and mortality was 2%. Among patients with S-lactate  $\geq$  4.0 mmol/l, 56% were admitted to ICU and 34% died. CRP was found not to be a predictor for intensive care and death. There was no significant correlation between initial CRP and S-lactate concentrations.

**Conclusions:** We saw a rising trend of iGAS 2008 – 2013, with incidence peaks during winter and spring, and the main focuses were soft tissue and lung. Elderly and patients with major comorbidities were in the majority, but also young and healthy were affected. Initial S-lactate, but not CRP concentrations, was a predictor for disease severity.

**Key words:** invasive group A Streptococcal infection, intensive care, lactate, CRP, antibiotic treatment, mortality, pneumonia.

## **BACKGROUND**

### **Epidemiology**

The bacteria *Streptococcus pyogenes*, synonym with B-hemolytic group A Streptococcus (GAS), causes a wide range of infections, practically only in humans. They vary from harmless or moderate as impetigo and pharyngitis, to severe and sometimes life threatening as erysipelas with septicemia, necrotizing fasciitis and streptococcal toxic shock syndrome. Furthermore, analyses have shown that 12% of children older than five years are healthy carriers of GAS, compared to 4% among younger children and adults (1) (2). It is difficult to distinguish between healthy carriers and individuals with subclinical infection or GAS carriers with a viral infection. This knowledge is important to consider when deciding if antibiotic therapy is necessary. Despite several studies, there is still no consensus how to interpret positive tests with clinical findings (3). Other facts to take into account when deciding whether therapy is necessary or not, is that individuals with positive rapid-test for GAS but no clinical presentation may infect people in their surrounding.

Among the many clinical presentations of iGAS, soft tissue infections are common.

Necrotizing fasciitis and myositis are very severe conditions where the muscular fascia or the muscles are affected, and the disease often has a quickly developing course from the first symptom to life threatening status with septicemia and sometimes Streptococcal toxic shock syndrome. “Pain out of proportion” to local status are typical clinical signs and a wound for bacterial entrance is not always identified (4).

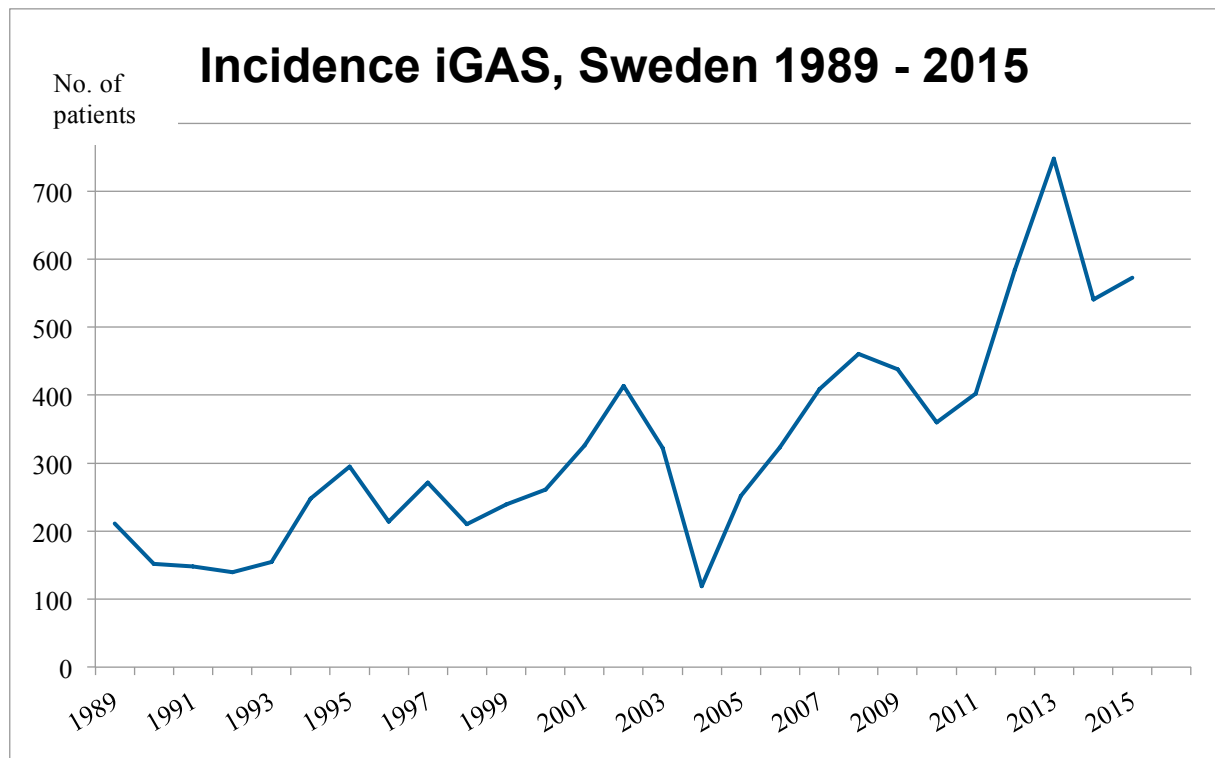
Another clinical entity is Streptococcal toxic shock syndrome (STSS) which may occur without soft tissue infection. It was in 1993 defined as a state of hypotension (for adults, systolic pressure  $\leq$  90 mmHg) together with two or more organs affected. That could include kidneys, liver, coagulation, lungs (ARDS, acute respiratory distress syndrome) and necrotizing soft tissue (5).

GAS infection is a transmittable disease but there are no clear-cut epidemic outbreaks. The bacteria spread either directly from human to human, indirectly via objects, or as a droplet infection. Incubation period is one to three days.

Complications after GAS infections have changed over time. Rheumatic fever, acute glomerulonephritis and puerperal fever are complications used to be associated with GAS infections, but are rare in Sweden now days. A common thought is that introduction of antibiotics changed the panorama of complications, but the decline started before the introduction of penicillin. There are several theories about the causes (for rheumatic fever i.e. nutrition, hygiene, access to medical care, and the degree of crowding in households, virulence of bacterial strains) but conclusive knowledge is limited on those circumstances (6)

*Streptococcus pyogenes* have several serotypes and can be differed by both T-typing and M-typing. Those classification systems reflect the presence of different bacterial surface proteins and M-type analysis is Swedish laboratories' standard since 2012. The M protein, which is

encoded by the *emm* gene, is an important virulence factor, and to date around 150 different M-types are characterized (7). Serotype prevalence varies over time, between regions and countries, and is of interest for epidemiological research on GAS and iGAS worldwide (8-14).



**Figure 1. iGAS incidence in Sweden 1989 – 2015.** A rise in incidence of iGAS has been notified in Sweden since the mid 80's. The reason is not fully understood. Data collected from [folkhalsomyndigheten.se](http://folkhalsomyndigheten.se) (15)

Since 1st July 2004, reporting invasive group A streptococcal infection is compulsory, according to the Communicable Diseases Act (Smittskyddslagen). Both the clinic and the laboratory are obliged to report all cases of iGAS (defined as positive culture from a sterile compartment) to the Institute for Communicable Diseases (Smittskyddsinstitutet) via [sminet.se](http://sminet.se). “Probable STSS” is also obliged to be reported, defined as an image of STSS and positive GAS-culture from a non-sterile compartment, e.g. soft tissue. In Sweden a rise in incidence of iGAS has been notified since the mid 80's, and the reason for this is not fully understood (15). (Fig 1)

Prognostic markers to identify patients with the highest risk for severe disease and need of intensive care are not well defined. Concentrations of blood lactate and C-reactive protein concentrations have been suggested to be such markers in many clinical settings.

### **Diagnose**

Various combinations of clinical symptoms, positive culture, positive “rapid strep test” and detection of bacterial DNA provide help to diagnose GAS infections. Invasive GAS infection is confirmed by positive culture from a sterile compartment such as blood, cerebrospinal fluid or joint fluid. Even though there sometimes is no positive culture from a sterile compartment, invasive GAS infection is still used in clinical settings as diagnose based on clinical symptoms, e.g. patients with erysipelas with severe sepsis or septic shock.

For definition of severe sepsis and septic shock the following criteria based on the SIRS concept was used by clinicians:

### **Definitions**

Systemic Inflammatory Response Syndrome (SIRS) is an inflammatory response from the immune system, with or without infection. SIRS is defined as 2 or more of the following 4 criteria:

- Body temperature above 38 centigrade or below 36 centigrade
- Heart rate above 90 beats/min
- Respiratory rate above 20 breaths/min or  $pCO_2 < 4.2$  Pka
- Leucocyte concentration  $> 12$  mmol/l or  $< 4$  mmol/l or 10% immature cells

### Sepsis:

- SIRS caused by infection

### Severe sepsis:

- Sepsis and hypo perfusion / organ dysfunction / hypotension. (see definitions below)

### Septic shock:

- Severe sepsis with hypotension, that does not respond to proper fluid substitution and
- Hypo perfusion / organ dysfunction (see definitions below)

### *Hypotension:*

- ❖ Systolic blood pressure < 90 mmHg or need of vasoactive medication to maintain > 90 mmHg.

### *Hypo perfusion:*

- ❖ Base excess < or = -5 and lactate < 1 mmol/l above the highest normal value.

### *Organ dysfunction:*

- ❖ CNS: acute change in mental status (e.g. confusion)
- ❖ Respiration:
  - pO<sub>2</sub> < 7.0 kPa (= sat 86%) or pO<sub>2</sub> < 5.6 kPa (= sat 78%) if focus for infection is lung.
  - pO<sub>2</sub>/FiO<sub>2</sub>, < 33 or < 27 if focus for infection is lung.
- ❖ Renal: oliguria, < 0.5 ml/kg/h despite proper volume supply
- ❖ Hepatic: S-bilirubin > 45micromol/l
- ❖ Hematologic: thrombocytes < 100 x 10<sup>9</sup>/l, PK/INR >1,5 or APTT > 60 sec (16)

### **Treatment**

Healthy carriers of GAS and harmless infections such as impetigo are often left without systemic antibiotic treatment. Pharyngitis/tonsillitis and moderate skin- and soft tissue infections are treated with oral antibiotics, often with ordinary penicillin. Patients with invasive infection need immediate treatment with intravenous antibiotics and often also intravenous fluids to avoid or treat shock and organ failure. In some cases intensive care with mechanic ventilation and/or dialysis is needed. There are also a few other options described below. For patients with necrotizing fasciitis surgery is often lifesaving.



*Streptococcus pyogenes* is a gram-positive cocci, sensitive to several antibiotics.

1<sup>st</sup> choice of antibiotics is ordinary Penicillin. For oral treatment that is phenoxymethylpenicillin (PcV) and for intravenous treatment benzylpenicillin (PcG). The difference between those two is that the PcV-molecule has an oxygen atom making it more stable to gastric acid, leading to possible treatment per os (17). PcG is given parenterally and therefore results in higher tissue concentrations and more efficient antibacterial effects. Up to date, there is no resistance development to Penicillin. Second choice, for instance to patients with allergy to penicillin, is usually clindamycin, erythromycin or cephalosporins.

Clindamycin is 1<sup>st</sup> choice in case of allergy towards penicillin and/or cephalosporins, but otherwise restrictions should be applied, due to risk of developing *Clostridium difficile* infection. In severe infections, though, clindamycin is often added to penicillin since the combination has some advantages. Those advantages are related to its mechanism.

Clindamycin blocks the bacteria's protein synthesis at a ribosomal level, which is not affected by the activity of the bacteria, as for penicillin's mechanism. In case of larger infectious inoculate sometimes GAS enter a phase of lower activity, hence clindamycin might be more efficient than penicillin, because the binding protein for penicillin on the bacteria's surface is then down regulated (18). Furthermore, a combination of a beta-lactam antibiotic acting on the cell wall and an antibiotic effective on the ribosomal level might be an advantage.

Clindamycin is not affected by the size of the inoculate, as described above, and also have a longer half-life that might contribute (19).

Intravenous cephalosporins, e.g. cefotaxim, are often prescribed septic patients with unknown focus and/or etiology, to cover up for gram-negative bacteria. Oral cephalosporins are also used as treatment for mild or moderate streptococcal reinfections, e.g. tonsillitis.

Erythromycin, and other macrolides, is sometimes recommended for GAS-reinfections.

However, in late 90's and early 00's GAS showed developing resistance toward erythromycin. In contrary, that was connected to certain M/emm-types that were more prevalent at the time. Between 2005 and 2012 those serotypes declined, and so did the resistance (20). Still, the Medical Product Agency (Läkemedelsverket) recommend that macrolides should not be used for GAS infections, due to risk for developing resistance(21).

Intravenous immunoglobulins (ivIg) are sometimes tried out as additional treatment for the severely ill patients, especially those with severe fasciitis and myositis with or without streptococcal toxic shock syndrome (22) (23). IvIg wields its effect through several mechanisms, including neutralizing super antigens, inhibiting complement activation and facilitating opsonizing of bacteria. By adding ivIg the inflammatory cascade is generally inhibited (23). Prospective randomized clinical studies are, however, lacking.

Hyperbaric oxygen therapy (HBO) is also sometimes used as additional treatment, even though there are no controlled studies that conclude better survival or less need of surgery. HBO leads to vasoconstriction and anti-inflammatory effects leading to less edema, less growth of bacteria and blocking of toxins. Furthermore, as a result of HBO, leukocytes kill bacteria more effectively (in vitro) and oxygen tension rises in ischemic threatened tissue (24).

Despite quick and adequate access to intensive care, mortality is relatively high among patients with severe invasive infection such as necrotizing fasciitis and streptococcal shock syndrome. A European study comparing iGAS infections in 11 different countries 2003-2004 found that the overall mortality within 7 days for iGAS was 19%, necrotizing fasciitis 32 %, and for STSS 44%. For patients with necrotizing fasciitis surgery is lifesaving and often multiple sessions are needed (25).

## **Implication and aim**

iGAS causes severe and fatal infections. The national trend is a rising incidence, that up to date hasn't been explained. The aim of this study was to investigate epidemiological, clinical and treatment data on iGAS-patients at the University Hospital of Sahlgrenska in Gothenburg January 2008 – June 2013. Some specific question raised were: What are the main focuses for invasive infections? Are there any seasonal variations? How high is the mortality? How many patients need intensive care? Can we define predictors for patients who require intensive care or for whom outcome will be fatal?

## **SPECIFIC OBJECTIVES**

*First:*

- Survey on age, sex, seasonal variation, co-morbidity, focus for infection, location of positive culture, intensive care admission, treatment and survival less than one month from hospital discharge.

*Second:*

- Is CRP at arrival to the emergency room a predictor for intensive care and death?
- Is serum-lactate at arrival to the emergency room a predictor for intensive care and death?
- Is there a correlation between CRP and S-lactate concentrations at arrival to the emergency room?

## **MATERIAL AND METHODS**

### **Study population**

Patients older than 18 years of age, treated for iGAS (see definition below) at Sahlgrenska University Hospital, Gothenburg between 1<sup>st</sup> January 2008 and 30<sup>th</sup> of June 2013. All data were retrospectively collected from the patients' medical record.

## **Definition of iGAS**

Two definitions.

1. Positive culture from a sterile compartment *or*
2. Patients with at least one of the following diagnosis in their medical record, coded by the ICD-10 system.

- a) A40.0 Sepsis due to streptococcus, group A *or*
- b) M72.6 Necrotizing fasciitis, caused by group A streptococcus

## **Study design**

We conducted a retrospective medical record review. One person collected all data from the patients' medical record in the data base Melior and software connected to Melior such as ELVIS, LabBest and scanned documents, and filed it in an excel document where all patients received a code for anonymization.

## **STATISTICAL METHODS**

We used the software SPSS for all analyses. Descriptive analyses were used for the first aim. For the second we conducted Fisher's Exact Test for S-lactate as predictor for ICU and death, and for CRP the corresponding analysis was chosen to be a simple boxplot. Pearson's analysis was used for calculation of linear correlation between CRP and S-lactate.

## **ETHICS**

All patients were coded anonymized. The coding key was kept separate from patient data. Permission from the Ethical Committee University of Gothenburg to collect data from the medical records was obtained and is attached as Appendix 1.

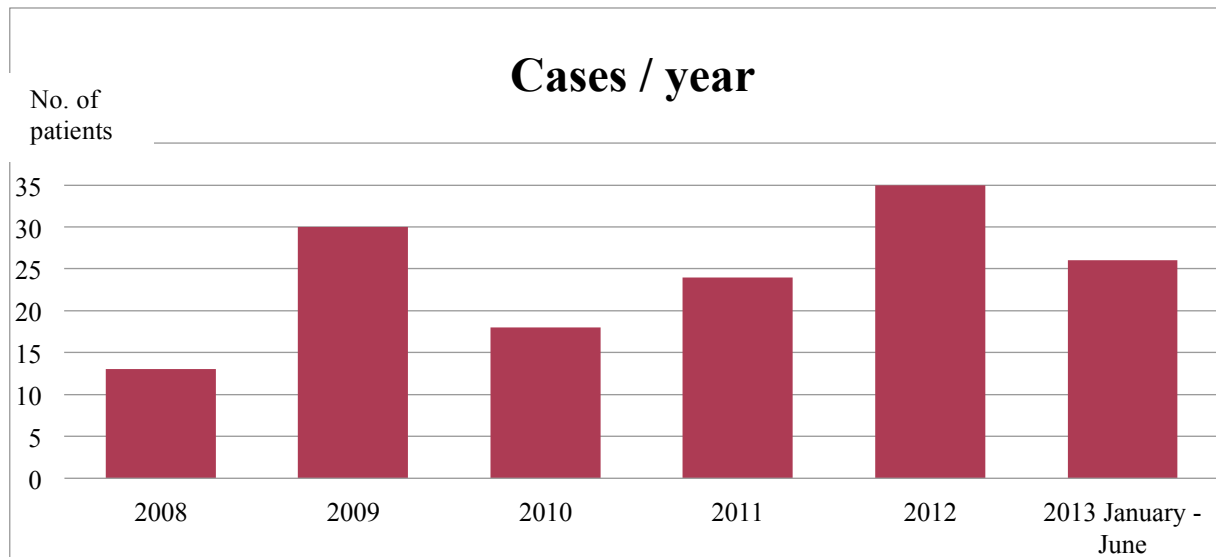
## RESULTS

### Patient characteristics

We identified 146 patients treated for invasive beta-hemolytic group A streptococci bacteria at Sahlgrenska University Hospital between 1st January 2008 and 30th June 2013. Sixty (41%) were women and eighty-six (59%) were men. Age varied from 18 to 99 with a median of 61 years. Ninety-four (64%) patients had any kind of major co-morbidity. Circulatory disease was the most prevalent (n=45) followed by diabetes mellitus (n=32) and pulmonary disease (n=23). Forty-seven (32%) patients had no co-morbidity reported. (Table 1)

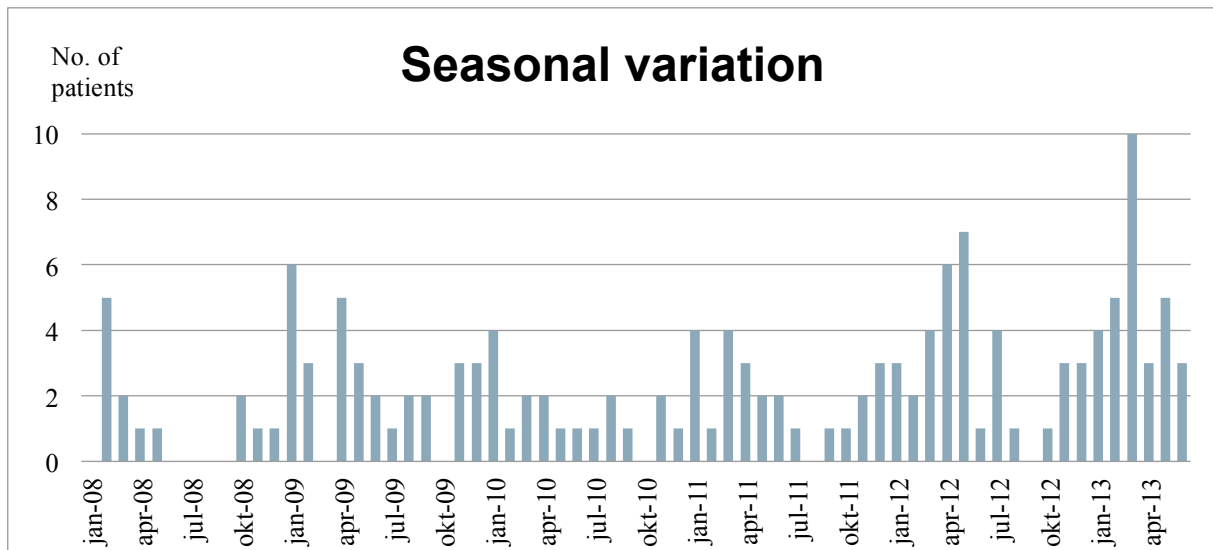
**Table 1. Patient characteristics for all included in this study.** Data was collected from medical records, after ethical permission. We identified 146 patients treated for invasive beta-hemolytic group A streptococci bacteria at Sahlgrenska University Hospital between 1st January 2008 and 30th June 2013. Sixty (41%) were women and eighty-six (59%) were men. Age varied from 18 to 99 with a median of 61 years. Ninety-four (64%) patients had any kind of major co-morbidity. Circulatory disease was the most prevalent (n=45) followed by diabetes mellitus (n=32) and pulmonary disease (n=23). Forty-seven (32%) patients had no co-morbidity reported.

	All patients (n = 146)	Admitted to Intensive Care Unit (n = 41)	Dead within 1 month after hospital discharge (n = 17)
Women	41% (n=60)	29% (n=12)	29% (n=5)
Men	59% (n=86)	71% (n=29)	71% (n=12)
Age, median	61 y. (18-99)	55 y. (34-91)	79 y. (41-99)
No major comorbidity	32% (n=47)	49% (n=20)	24% (n=4)
Major co-morbidity, any	68% (n=99)	51% (n=21)	76% (n=13)
Circulatory	31% (n=45)	20% (n=8)	71% (n=12)
Diabetes	22% (n=32)	10% (n=4)	6% (n=1)
Pulmonary	16%(n=23)	12% (n=5)	29% (n=5)
Renal	9% (n=13)	5% (n=2)	12% (n=2)
Liver	5% (n=8)	5% (n=2)	0% (n=0)
Malignancy	11% (n=16)	3% (n=1)	12% (n=2)
Immunosuppression	5% (n=8)	5% (n=2)	6% (n=1)

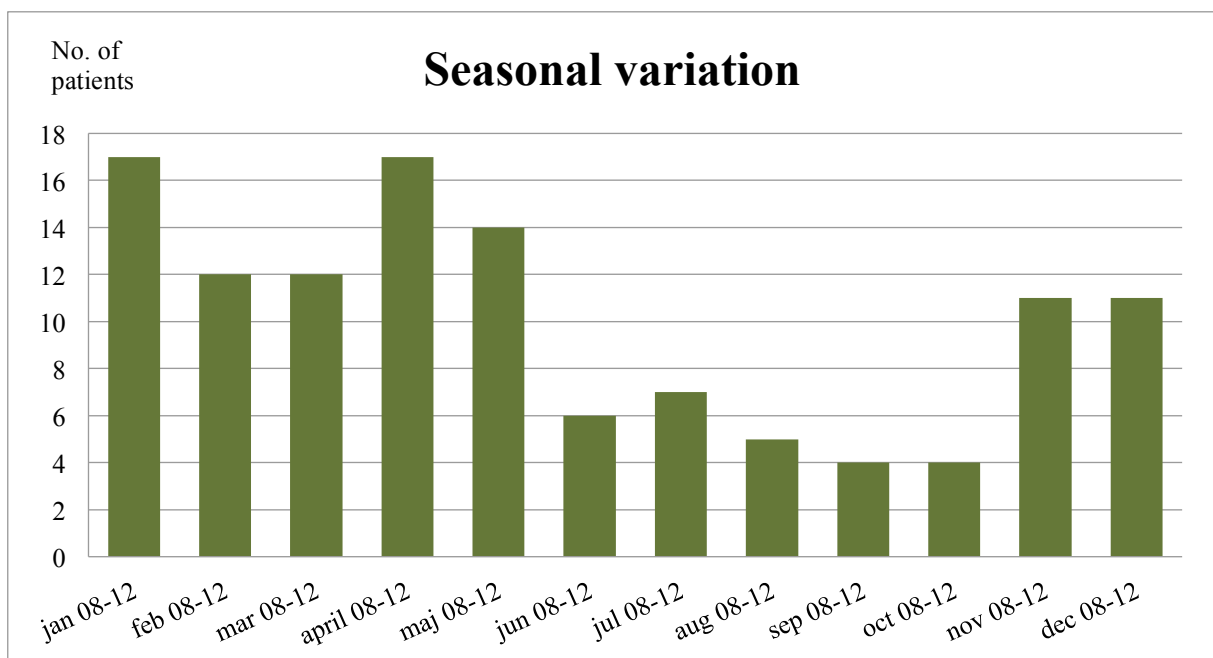


**Figure 2. Cases of invasive group A streptococcal infections per year at Sahlgrenska University Hospital, January 2008 – June 2013.** For 2013 only January – June is reported due to the timing of data collection of this study. The numbers represent patients in this study identified by either 1. Positive culture from a sterile compartment or 2. At least one of the following diagnoses in their medical record. A40.0 Sepsis due to streptococcus, group A or M72.6 Necrotizing fasciitis, caused by group A streptococcus.

## Seasonal variation



**Figure 3. Seasonal variation of invasive group A streptococcal infections at Sahlgrenska University Hospital per month, Jan 2008 - June 2013.** For 2013 only January – June is reported due to the timing of data collection of this study. Month and year was defined by which day they attended the clinic. The numbers for each month represent patients identified by either 1. Positive culture from a sterile compartment, or 2. All patients were diagnosed with either A40.0 Sepsis due to streptococcus, group A or M72.6 Necrotizing fasciitis, caused by group A streptococcus.



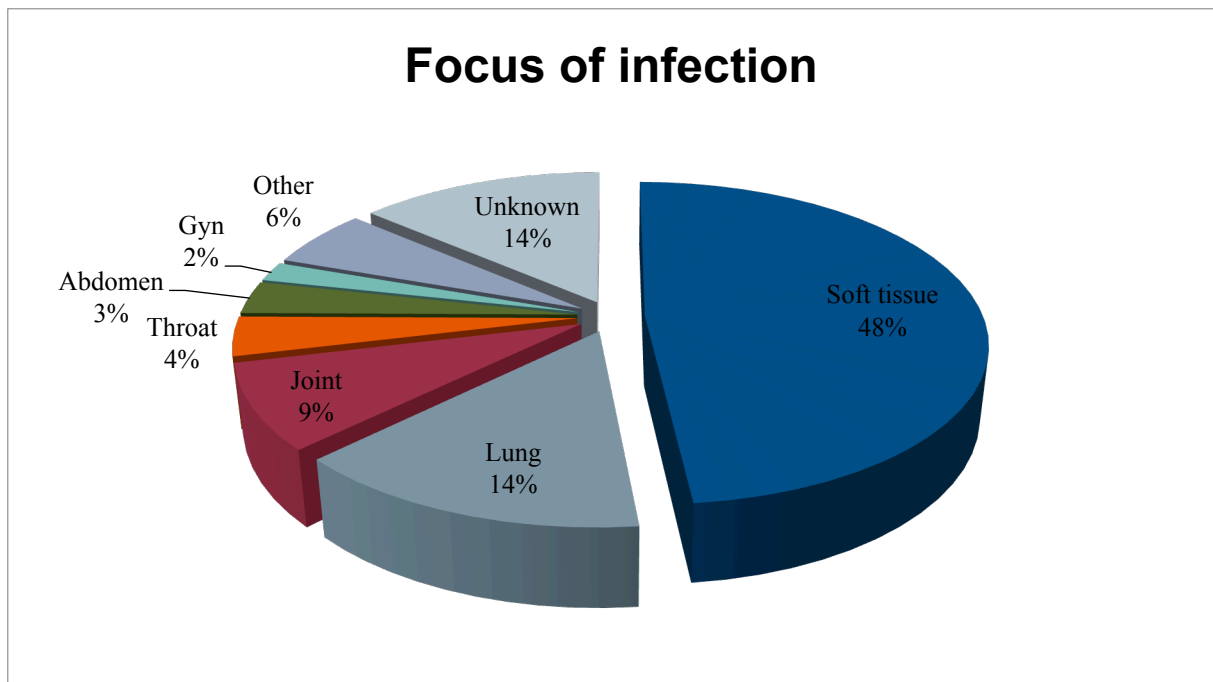
**Figure 4. Seasonal variation of invasive group A streptococcal infection at Sahlgrenska University Hospital, January 2008 - June 2013, compiled per month.** For 2013 only January – June is reported due to the timing of data collection of this study. Month and year was defined by which day they attended the clinic. The numbers for each month represent patients identified by either 1. Positive culture from a sterile compartment, or 2. Diagnosed with either

*A40.0 Sepsis due to streptococcus, group A or M72.6 Necrotizing fasciitis, caused by group A streptococcus.*

### Focus of infection

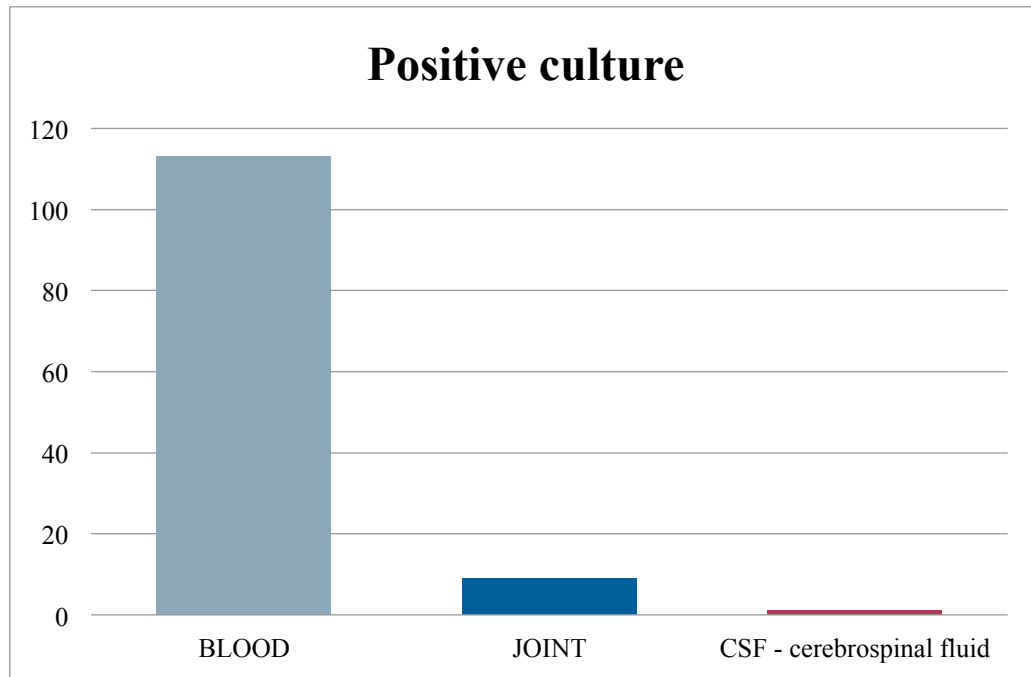
Some patients had more than one focus of infection, therefore the numbers in Figure 5 doesn't correspond with those described in the text below.

The most prevalent focus of infection was soft tissue (n=74) (60% of the patients). Two of those patients had necrotizing fasciitis. The second most prevalent focus was lung (n=22) (15% of the patients) followed by unknown (n=21) (14% of the patients).



**Figure 5.** *Focus of invasive group A streptococcal infection at Sahlgrenska University Hospital January 2008-June 2013. For 2013 only January – June is reported due to the timing of data collection of this study. Percentage numbers represent the share of infection focuses (positive cultures), not percentage of patients. Some patients have more than one focus, and therefore the total numbers of infection focuses reported are more than the total number of patients. Focuses were identified by “positive culture” in the patients’ medical record.*





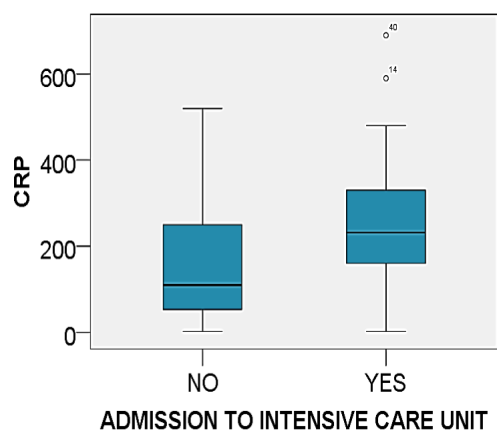
**Figure 6. Positive bacterial cultures from sterile compartments.** *Data on positive culture from sterile compartments were identified in the patients' medical record. We found 113 positive cultures in blood (77%), 9 in joint (6%) and 1 in cerebrospinal fluid (1)*

In sterile compartments we found 113 positive cultures in blood (77%), 9 in joint (6%) and 1 in cerebrospinal fluid (1%) (Fig 6). Even if there was no positive culture from any sterile compartment in 25 cases (17%) and the invasive infection diagnosis was made on clinical grounds, 20 of these patients had positive culture from soft tissue (wound or tissue) confirming they suffered from a group A streptococcus infection. The remaining 5 cases, lacking positive cultures from sterile compartments have not been further investigated and are until now seen as primary sepsis of unknown focus. Totally, soft tissue cultures were positive in 53 cases (36%), throat culture in 5 cases (4%) and in 15 cases (10%) there was a positive culture from other locals, few and diverse and therefore not presented.

#### **CRP as predictor of intensive care and death**

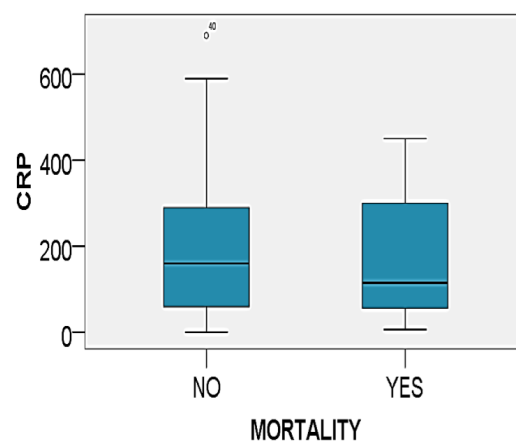
The 50% confidence interval of initial CRP was partly overlapping between those who were admitted to intensive care unit (ICU) than those who were not. The median CRP value was

higher for patients admitted to ICU than for non-ICU patients. The overall highest CRP value was slightly higher in the non-ICU group (Fig 7). The 50% confidence interval of initial CRP was completely overlapping between those who died within 1 month from hospital discharge and those who didn't. The median CRP value was higher for survivors than for non-survivors. The overall highest CRP values were found in the survivors' group. (Fig 8)



**Figure 7. Comparing initial CRP levels of two groups with different outcomes according to Admission to intensive care unit.**

*YES = admitted to intensive care unit.  
NO = not admitted to intensive care unit.  
The blue box contains 50% of patient data. The line on each side of the blue boxes, parallel to the y-axis, represents the higher and lower 25% of patient data. Between the two horizontal lines are the total range of CRP-values represented. The line across the blue box is the median value.*



**Figure 8. Comparing initial CRP levels of two groups with different outcomes according to 1 month mortality**

*YES = died within 1 month.  
NO = 1 month survivors.  
The blue box contains 50% of patient data. The line on each side of the blue boxes, parallel to the y-axis, represents the higher and lower 25% of patient data. Between the two horizontal lines are the total range of CRP-values represented. The line across the blue box is the median value.*

### S-lactate as predictor of intensive care and death

Among all patients who had a S-lactate registered (n=102) 34% (n=35) were admitted to ICU and 14% died within one month. Patients with initial S-lactate <2 mmol/l were never admitted to ICU, however, 7% (n=2) in this group died. In the intermediate group (lactate between 2.0-

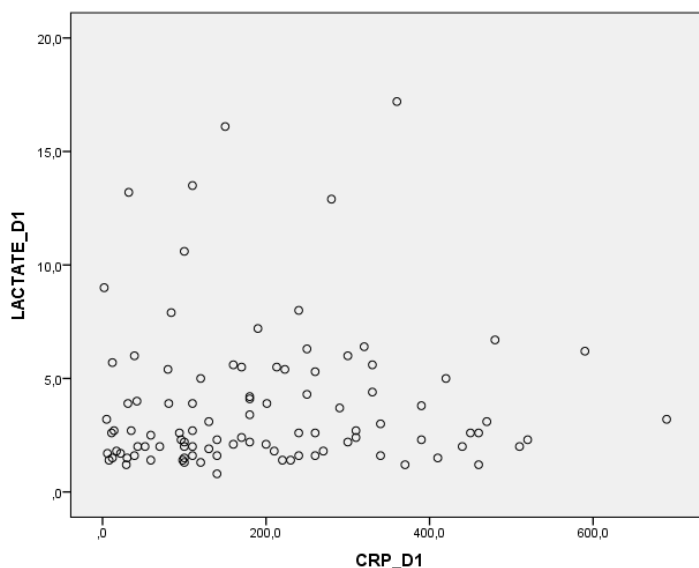
3.9 mmol/l) 39% (n=17) were admitted to ICU and mortality was 2% (n=1). In the high S-lactate group (lactate above 4.0 mmol/l) significantly more patients 56% (n=18) were admitted to ICU and 34% (n=11) died.  $p < 0.001$  for both analysis. (Table 2)

**Table 2. Initial S-lactate concentrations, admission to intensive care unit and mortality.** Among all patients who had a S-lactate registered (n=102), 34% (n=35) were admitted to ICU and 14% died within one month. Patients with initial S-lactate <2 mmol/l were never admitted to ICU, however, 7% (n=2) in this group died. In the intermediate group (lactate between 2.0-3.9 mmol/l) 39% (n=17) were admitted to ICU and mortality was 2% (n=1). In the high S-lactate group (lactate above 4.0 mmol/l) significantly more patients 56% (n=18) were admitted to ICU and 34% (n=11) died.

S-lactate (mmol/L)	Admission to Intensive Care Unit		Mortality within 1 month		Total (n)
	Count	Percent	Count	Percent	
< 2.0	0	0%	2	7%	27
2.0 – 3.9	17	39%	1	2%	43
> 4.0	18	56%	11	34%	32
<b>Total</b>	<b>35</b>	<b>34%</b>	<b>14</b>	<b>14%</b>	<b>102</b>

### Correlation between initial CRP and initial S-lactate

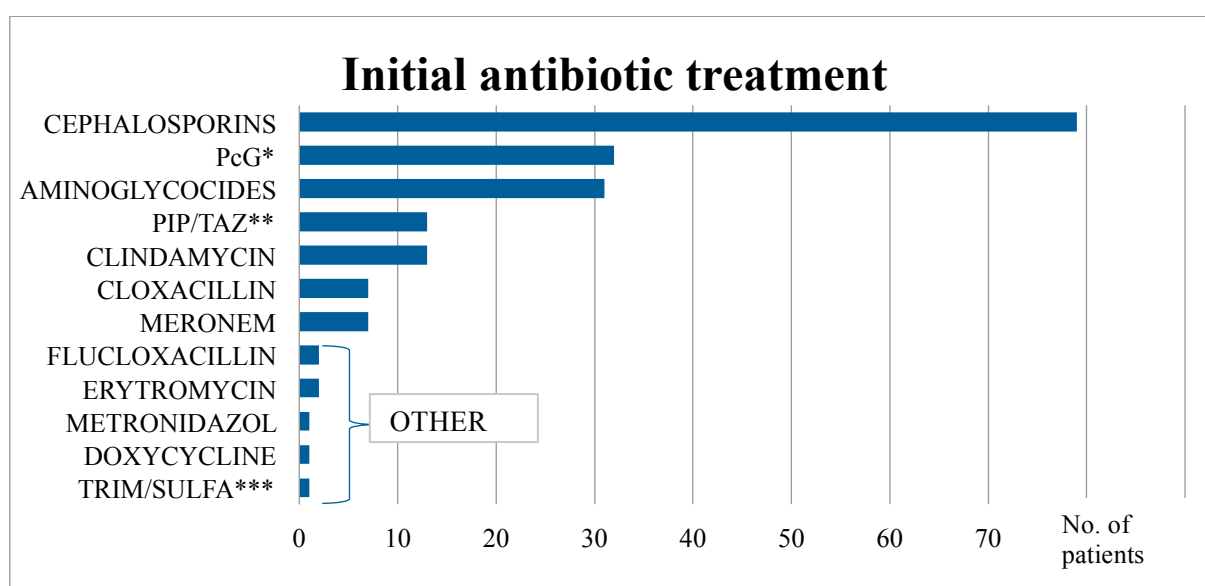
Spearman’s correlation analysis showed no significant correlation between initial CRP concentrations and S-lactate (n=102). Correlation coefficient: 0.131,  $p > 0.05$  (Fig 9)



**Figure 9. Correlation between initial CRP and initial S-lactate.** Spearman's correlation analysis showed no significant correlation between initial CRP concentrations and S-lactate (n=102). Correlation coefficient: 0.131,  $p > 0.05$

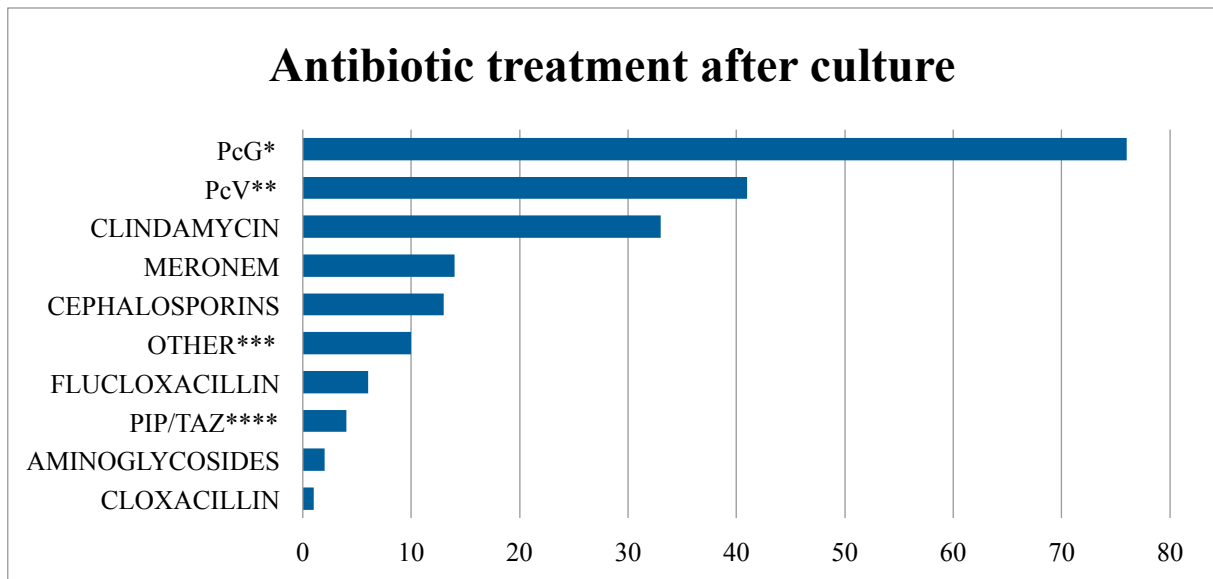
## Antibiotics

The most frequently used antibiotics, before culture results were known, were cephalosporins (n=79) (54%), PcG (n=32) (22%) and aminoglycosides (n=31) (21%) Treatment was given in different combinations and sometimes as mono therapy (Fig 10).



**Figure 10. Initial antibiotic treatment, i.e. before receiving the bacterial culture result.** Patients often received more than one type of antibiotics. The most frequently used initial antibiotics were cephalosporins (n=79) (54%), PcG (n=32) (22%) and aminoglycosides (n=31) (\*Benzylpenicillin \*\*Piperacillin/Tazobactam \*\*\*Trimetoprim/Sulfametoazol)

After culture results were known, PcG was the most frequently used antibiotic (n=76) (48%) followed by PcV (n=41) (28%) and clindamycin (n=40) (27%). As for initial antibiotics, after culture results were known, treatment was given in different combinations and/or as mono therapy (Fig 11). Antibiotic therapy was for some patients shifting more than once after their result was known.



**Figure 11. Antibiotic treatments after bacterial culture results.** Patients received more than one antibiotic in some cases. After culture results were known, PcG was the most frequently used antibiotic (n=76) (48%) followed by PcV (n=41) (28%) and clindamycin (n=40) (27%). After culture results were known, treatment was given in different combinations and/or as mono therapy.

\* Benzylpenicillin \*\*Phenoxymethylpenicillin \*\*\*Antibiotics defined in Figure 10

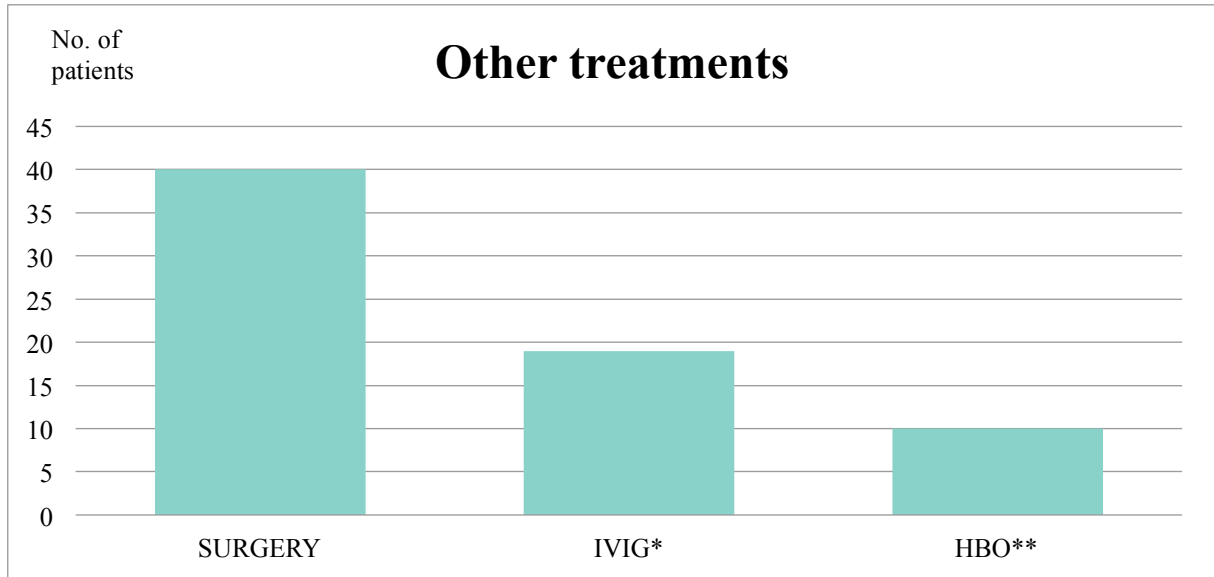
\*\*\*\*Piperacillin/Tazobactam

#### Other treatments

**Surgery:** Surgery was performed in forty patients (28%), ranging from 1 to 9 sessions with a mean of 3 times and a median of 2 times. (Fig 12)

**IVIg:** Nineteen patients (13%) received intravenous immunoglobulin, ranging from 1 to 4 days with a mean of 2.2 and a median of 2 days. Seven patients who were treated with ivIg died, and opposite, of those 17 who died 7 got ivIg treatment. All patients, except for one, who received ivIg were intensive care unit patients. No data of dosage collected. (Fig 12)

**HBO:** Ten patients (7%) received hyperbaric oxygen therapy, ranging from 1 to 6 sessions with a mean of 3.5 times and a median of 3.5 times. (Fig 12)



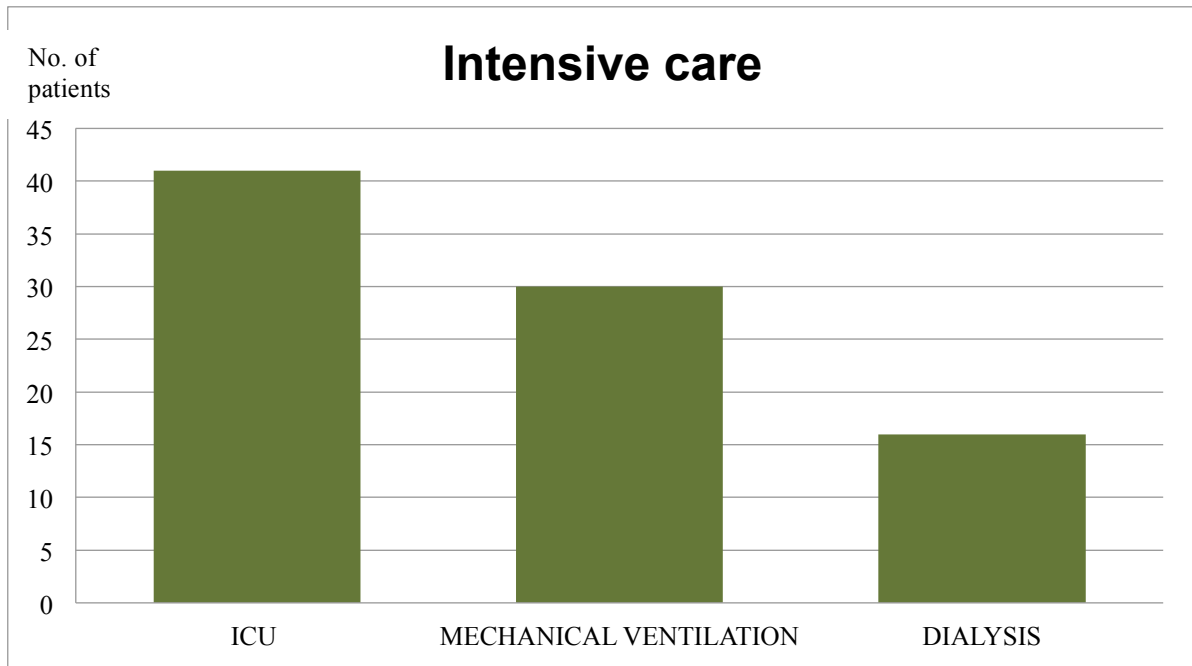
**Figure 12. Number of patients receiving additional treatment beside antibiotics.**

**Surgery** was performed in forty patients (28%), ranging from 1 to 9 sessions with a mean of 3 times and a median of 2 times. Nineteen patients (13%) received **ivIg\***, ranging from 1 to 4 days with a mean of 2.2 and a median of 2 days. Seven patients who were treated with **ivIg\*** died, and opposite, of those 17 who died 7 got **ivIg** treatment. All patients except for one, who received **ivIg**, were intensive care unit patients. No data of dosage collected. Ten patients (7%) received **HBO\*\***, ranging from 1 to 6 sessions with a mean of 3.5 times and a median of 3.5 times.

\*Intravenous immunoglobulin \*\* Hyperbaric oxygen therapy

### Intensive care

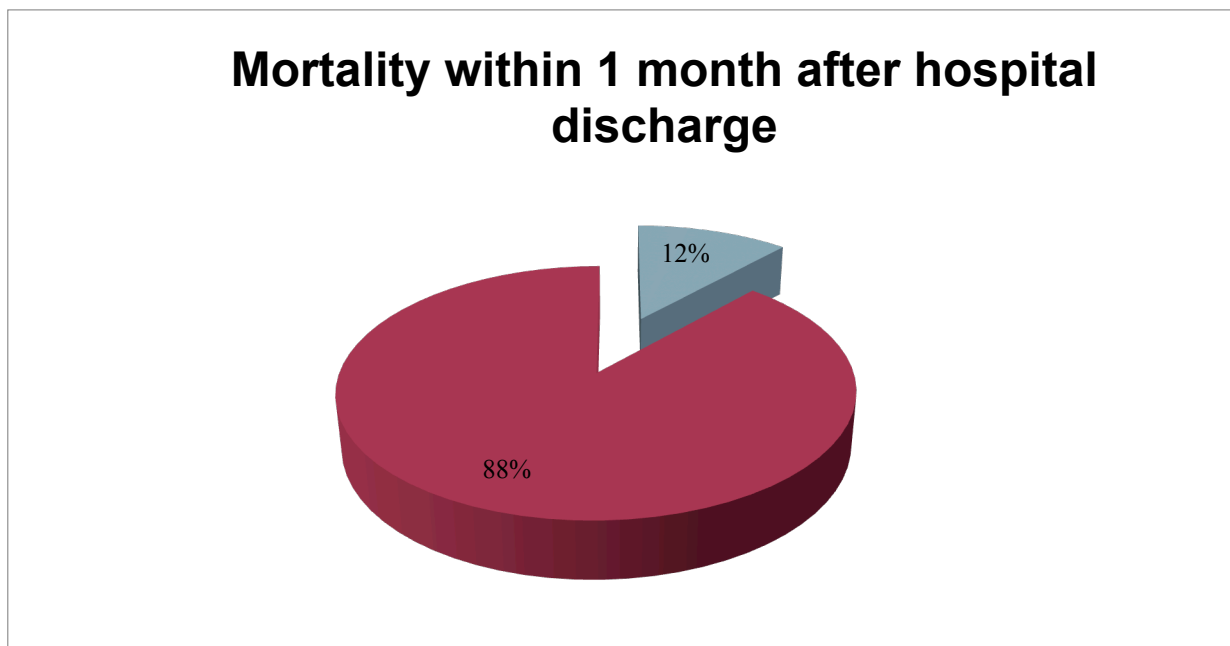
41 patients (28.3%) received intensive care. For 30 patients of those 41, that included mechanical ventilation and for 16 patients it included dialysis. (Fig 13)



**Figure 13. Patients admitted to Intensive Care Unit.** Forty-one (of 146) patients were admitted to Intensive Care Unit (ICU). Thirty of those received mechanical ventilation and 16 needed dialysis.

#### Mortality

17 (12%) of 146 died within 1 month after hospital discharge of whom nine (53%) patients did not receive intensive care.



**Figure 14 Mortality rate.** Seventeen (12%) patients included in this study died within one month after hospital discharge of whom nine patients (53%) did not receive intensive care.

## **DISCUSSION**

The increasing number of invasive streptococcal infections during the last 30 years in Sweden is worrying and difficult to explain. In our study, a similar tendency of increasing number was observed as in the national report and linked to the dark half of the year, with focus of infections mainly from the soft tissue although lung focus was surprisingly common. There exist several theories explaining the increasing incidence such as new virulent bacterial strains, bacterial strains in a population that lack local immunity, and crowding of children in day care center resulting in a large bacterial pool in the society.

### **Seasonal variation**

Most infections occurred between November and May, as found in previous studies (25). This finding support the crowding theory since it is during this time of the year that most children are indoors and closer to each other than during the half-year with better climate.

Furthermore, the influenza season is concurrent with the high incidence period in our study, and, as Barnham clarifies it is already known that “Acute viral tract infections can be associated with the occurrence of *S. pyogenes* pneumonia, reflecting virus-induced epithelial damage in the respiratory tract together with transient immune suppression” (26) In conclusion, the high and low season for iGAS infections were anticipated since this pattern is previously observed and stable since decades ago.

### **Focus**

The most prevalent focus of infection was soft tissue, in more than half of the patients. The second most prevalent focus was lung followed by unknown. There were only exceptional cases with focus from the throat. This distribution is in agreement with previous observations(27).



## **Focus – lung**

A decline in *Streptococcus pyogenes* community acquired pneumonia has been observed since the clinical introduction of penicillin in 1942. Nevertheless, *S. pyogenes* is a pathogen that still causes severe and fatal lung infections, including the 22 patients in our study. A recent study showed a high mortality rate (20%) of *S. pyogenes* pneumonia, with half of the patients dying within 24 h after admission (28).

Surprisingly there have been few studies on *S. pyogenes* pneumonia more specifically since STSS was first described three decades ago. Muller et. al. published a large population-based study 2003(29). They found a higher case fatality rate for GAS pneumonia than for necrotizing fasciitis, 38% vs. 26%, highlighting its severity. Furthermore they pointed out that the high mortality and rapid progression occurred despite early appropriate antibiotic therapy and the use of advanced supportive measures, suggesting that interventions directed at the underlying pathogenesis of STSS will be required to improve outcomes. In 2003 intravenous immunoglobulin had recently been introduced in clinical settings but they had too few patients treated with ivIg to draw any conclusions. Still, 13 years later, there are no guidelines or sufficient studies on ivIg-treatment.

## **Focus - throat**

In our study throat represented 4% of all focuses, which is a small number according to the total incidence of GAS throat infections in society. GAS throat infection is not considered a common entry for iGAS infections, but Strömberg et al. found 12% of upper respiratory tract symptoms among their 97 inward patients with group A *Streptococcus* bacteremia in a Swedish national outbreak 1988 (30).

Are throat infections truly less invasive to the extent found in this study or are throat infections hidden in the rather large group of “Unknown”, which comprises 14% of the total

material in our study? Since our study is retrospective it is difficult to know if all clinical data has been asked for. One of our theories that might apply is that throat samples for culture or rapid test are less performed in infectious patients without an obvious focus at the emergency room compared with for example urine culture, reflecting the physician's lower expectation on throat being the focus of severe disease. Also, as Ekelund et al argue in their study from 2004 (31) where they investigate gastrointestinal symptoms as primary sign of severe invasive group A streptococcal infections, throat ache might not be noted at the emergency room due to the domination of gastrointestinal symptoms, caused by GAS toxins, or other symptoms.

Although throat rarely is the origin for severe disease it might transmit bacteria to other family members or people of close relations and for instance infect a wound. The Swedish national recommendations on handling of pharyngotonsillitis(32) is based on the Centor criteria(33), a clinical tool developed to help physicians decide whether to treat pharyngotonsillitis with penicillin (or other antibiotics) or not. At least for the last decade, it has been an ongoing argumentation against Centor criteria in favor of testing all patients with a sore and paining throat with either rapid test or culture, and then treat all patients testing positive for GAS. (34-36)

In this retrospective study it was not possible to analyze if there was any suspected GAS pharyngotonsillitis in the environment before the patient developed iGAS,. Since GAS is a common bacteria also in milder infections, it would require serotyping of both iGAS infections, milder GAS-infections and carriers to clarify the connection between mild and invasive infections.

## **Treatment**

Antibiotic treatment before etiology was confirmed, was dominated by cephalosporins, given in almost 50% of the patients, followed by PcG (22%) and aminoglycosides, often given as a

combination with these two. *Streptococcus pyogenes* is sensitive to both cephalosporins and PcG but resistant to aminoglycosides. Since decision on initial antibiotic treatment most often is taken on clinical grounds for community acquired septic patients of unknown etiology, it is reasonable that aminoglycosides were prescribed along with either cephalosporins or PcG to extend the gram-negative spectrum and to use its fast bactericidal effect.

After culture result was received, antibiotic pattern changed evidently towards narrower antibiotics such as PcG , PcV and clindamycin. Aminoglycosides and cephalosporins were now given only rarely. Some patients were still treated with a combination of antibiotics after culture, most commonly penicillin and clindamycin to use the different action of killing the bacteria, but also sometimes with meropenem that doubled from 3.5% to 7% of unknown reason.

### **Mortality**

17 patients (12%) died within one month from hospital discharge. Nine of those received intensive care and eight did not receive intensive care. Looking closer into data on deceased patients, it was clear that the non-intensive care group had severe co-morbidities and high age and probably it was for ethical reasons they weren't provided intensive care. However, these facts affect all analyses in this study concerning intensive care and mortality.

### **CRP and S-lactate as predictors for intensive care and death**

S-lactate, but not CRP concentrations, was a good predictor for disease severity.

For S-lactate it was clear that if you had an initial value  $< 2$  mmol/l you would not qualify for intensive care during the present period of disease. But two patients in this subgroup died within 1 month. Those two had three and four major comorbidities respectively. Hence, it falls in line with the reasoning above that some patient are very frail to begin with, having

limited chances to survive severe disease, even though their S-lactate levels were moderate in this case.

In the intermediate group, with S-lactate 2.0 – 3.9 mmol/l, 39% were admitted to intensive care unit and 2% died, saying that many in this interval required advanced interventions, and could also benefit from them.

In the high S-lactate group, S-lactate  $\geq 4$  mmol/l, there was a difference from the intermediate group primary according to mortality, with 34% in the high lactate group and 2% in the intermediate. This suggests that an intermediate S-level predicts benefit from intensive care in case you need it, whereas if you have a high lactate and need intensive care chances for a fortunate outcome is clearly lower, but no conclusions can be drawn from these comparison although they were significant with  $p < 0.001$  for both ICU admission and mortality.

Mikkelsen et. al. 2009 published a study on S-lactate's potential predictive value for 28-day mortality and found that initial serum lactate was associated with mortality independent of organ dysfunction in this study of emergency department patients with severe sepsis.

Furthermore, they demonstrated that the relationship between serum lactate levels and mortality was independent of the presence of clinically apparent shock. Therefore, serum lactate, in its association with mortality, did not seem to function solely as a marker of clinically apparent organ dysfunction or hypotension. (37, 38).

They also conducted a retrospective medical record review over septic patients at the emergency department, with all its strengths and limitations. For their statistic analyses they used logistic regression, that we also aimed to do, but since we didn't have sufficient patients in each group we failed, and had to shift to another method, the Fisher's Exact Test. Hence, the results are not as easy to compare as if we could have used logistic regression. Their question was also partly another since they compared patients with and without shock.

Despite those differences, some comparisons can be made. For example, they found that both intermediate and high serum S-lactate were predictive for 28-day mortality, but our results showed higher mortality only for high lactate patients. Another difference is that we had two patients in the low lactate group who died, whereas all their low lactate patients survived. Our results should be analyzed with some caution due to limited data, and more research should be done. (37) (Of additional interest is that only 109/147 had a S-lactate result in our records, suggesting S-lactate can be taken on wider indications) We agree with previous previous studies that a single serum lactate measurement provides useful information in patients with severe sepsis .

It is well known that  $CRP > 5$  is a good marker for inflammation, often with infectious etiology. To estimate the infection's severity though, CRP is of little help. It can even be a severe mistake trying to interpret the infection's severity based on CRP concentrations, as shown in our study. Since CRP mirrors the level of inflammation 24 hours ago and iGAS infections often develop very quickly, our results underline how important it is to follow the patient both clinically and with new laboratory analyses.

There was no correlation between CRP and S-lactate at arrival for patients in our study. Since we have concluded that initial S-lactate can be useful as predictor for disease severity and CRP is not an appropriate predictor for disease severity, it is reasonable that there was no correlation between those two markers.

### **The role of serotype for disease severity**

It has been debated why iGAS incidence increases. Many scientists investigate whether certain surface serotypes seem to comprise a greater virulence factor than others (8, 12, 17, 25, 39-42). Rogers et al also compare serotype incidence among severe infections with incidence of serotypes among mild infections and also with prevalence of carriers in the

community. They found that strain serotype prevalence, is the major factor responsible for an increase in serious group A streptococcus infections(13). They argue that the same serotype that causes many invasive infections also causes many mild infections and it is at the same time widely spread among carriers (13, 43). It would have been interesting to explore the local epidemiological circumstances on serotypes, but we had no possibility to look further into that, since the laboratory connected to Sahlgrenska University Hospital shifted from T-typing to M-typing during the period of our study, and as of equal importance, we had no control groups for M-typing from neither mild infections nor carriers.

### **Strengths and weaknesses**

Strengths with the study are that there is only one major hospital in the area making the patient material representative for the population and that all medical charts were entered and analyzed by the same person. We also had a fairly long follow up time. A weakness with the study is the retrospective approach. Medical records are sometimes vague and important data is missing. Patient history may miss the question about throat symptoms and if there were any GAS infections in the environment. Mortality and need of intensive care is sometimes more dependent on concomitant diseases than the iGAS infection. Furthermore, we were not able to analyze the serotypes.

### **CONCLUSIONS AND IMPLICATIONS**

We saw a rising trend of iGAS 2008 – 2013, with incidence peaks during winter and spring, and the main focuses were soft tissue and lung. Initial S-lactate, but not CRP concentrations, was a good predictor for disease severity. Elderly and patients with major comorbidities were in the majority, but also young and healthy was affected among both severe and fatal cases.

### **Further research**

There is a high severity rate of iGAS pneumonia and a low number of studies addressing that problem. It would be of interest and importance to look deeper in to the circumstances around the 22 pneumonia patients in this study, such as mortality, co-morbidity, development of disease, admission to intensive care and treatment. It would also be interesting to look closer into the soft-tissue infected patients data since they are the largest subgroup of patients. The fact that 40 patients received surgery but only 2 got necrotizing fasciitis diagnose raise i.e. the question whether necrotizing fasciitis is under diagnosed or not. Therefore surgical patients is another subgroup worth having a closer look upon.

## **POPULÄRVETENSKAPLIG SAMMANFATTNING**

### **Allvarliga infektioner med streptokocker grupp A i Göteborg 2008 - 2013**

Grupp A streptokocker (GAS) är en för människa sjukdomsorsakande bakterie som kan leda till infektioner i olika delar av kroppen och av olika svårighetsgrad. Exempel på lindrig infektion är svinkoppor, medelsvåra kan vara halsfluss, svåra kan vara rosfeber och mycket svåra kan vara lunginflammation eller muskelinfektion som även kan bli livshotande. När tidningarna skriver om ”mördarbakterien” eller ”den köttätande bakterien” är det oftast grupp A streptokocker det handlar om. De svåraste tillstånden inträffar när bakterien blir invasiv, vilket innebär att den tar sig till en lokal i kroppen som vanligtvis är helt steril, dvs. fri från bakterier. Den har då oftast tagit sig till blodet, men det kan även vara ledvätska eller ryggmärgsvätska.

Under senare år har antalet fall av allvarliga streptokock-infektioner ökat vilket motiverar denna tillbakablickande journalstudie på patienter med invasiv GAS-infektion. Man kan kalla det för en kartläggning av grundläggande data att ha som utgångspunkt för vidare

frågeställningar och forskning. Ålder (alla är över 18 år), kön, bakomliggande sjukdomar, infektionsfokus, ev. intensivvård, behandling inkl. antibiotikaval, laboratoriedata vid inläggning är sådant som jag har studerat. Tidsperioden är januari 2008 – juni 2013 och upptagningsområdet är Sahlgrenskas alla sjukhus i Göteborg.

Undersökningen visade att av 146 patienter så var 60 kvinnor och 86 män och medianåldern var 61 år. Ökningen man har sett i Sverige motsvaras av samma slags variation i Göteborg. Högsäsong för allvarliga GAS-infektioner låg mellan november och maj vilket är vanligt sannolikt för att både vuxna och barn vistas mera inomhus då, och då sprids bakterien lättare mellan människor. Att det är influensasäsong drabbar vissa särskilt hårt då de kan få först en influensainfektion och strax därefter en iGAS-infektion för att luftvägarna är skadade och immunförsvaret nedsatt. Nära 50% hade sin sjukdom i hud eller mjukdelar, men även lunginflammation var vanligt (14%). I lika många fall hittade man inte var infektionen hade sitt ursprung.

När patienterna kom in till sjukhus fick de antibiotika som är bra mot flera sorters bakterier, och sedan när man genom odling fått reda på vilken bakterie som orsakat sjukdomen bytte man ofta till mer specifika sorter. De flesta som blir allvarligt sjuka av invasiv GAS-infektion har en eller flera sjukdomar i botten, men även unga och friska kan drabbas hårt. Fyrtioen patienter behövde vårdas på intensivvården och 20 av dessa var friska sedan tidigare. Inom en månad efter utskrivning var det 17 patienter som dog, och fyra av dem var tidigare friska.

För att se om man har en infektion i kroppen är det vanligt att ta ett prov som heter CRP, eller snabbsänka som det ibland också kallas. Vi kunde bekräfta att det är ett prov som är bra på att påvisa infektionssjukdom, men som är dåligt på att säga hur allvarligt sjuk man är eller kommer att bli. Ett annat prov man kan ta är laktat, eller mjölksyrekoncentration, i blodet. Det är ett mycket bättre prov att använda när man försöker bedöma hur allvarligt sjuk en patient är



eller kommer att bli. Vid låga värden kan man känna sig trygg, men vid högre värden är det stor risk att man kommer behöva intensivvård och att man kanske kommer dö pga sjukdomen.

Det är alltså av värde att ta ett laktatprov för att kunna sätta in behandling tidigt i

sjukdomsförloppet för att utgången ska bli så bra som möjligt.

Mer forskning behövs på många områden när det gäller grupp A streptokocker, men vi vill särskilt lyfta fram behovet av forskning om lunginflammationer orsakade av GAS, mera forskning kring laktatets möjligheter att fungera som tidig varningssignal samt forskning kring ytterligare behandling vid sidan av antibiotika och intravenöst vätska, eftersom många blir svårt sjuka och dör trots att de tidigt får rätt sorts behandling.

## **ACKNOWLEDGMENTS**

Emelie Persson, for proofreading and support.

Lars Hagberg, for supervision.

## APPENDECIS

Regionala etikprövningsnämnden i Göteborg

Sida 1 av 2

**Projektansvarig:**  
Lars Hagberg  
Infektionskliniken  
SU/Östra  
416 85 Göteborg

**Dnr:**  
529-13

Exp. 2013-09-25  
*2013/11/2*

**Forskningshuvudman:** Västra Götalandsregionen

**Närvarande beslutande:**

Margit Kärrström, *ordförande*  
Sven Wallerstedt, *vetenskaplig sekreterare*

**Ledamöter med vetenskaplig kompetens:**

Ulf Angerås  
Daniel Holmgren  
Bodil Lemfelt  
Ulf Nilsson  
Birgitta Rembeck (*deltog ej i ärende 529-13*)  
Barbro Robertsson  
Elisabet Wennberg (*deltog ej i ärende 488-13, 527-13*)  
Maude Wikström

**Ledamöter som företräder allmänna intressen:**

Evert Eggelind  
Allaedin Hedayati  
Annelie Nielsen Fernström  
Anja Olsson  
Ros-Marie Sädås

**Granskad och godkänd som sekreterarärende  
Göteborg** *2013-11-22*

Sven Wallerstedt, professor, vetenskapl sekr  
Med avd 2  
Regionala etikprövningsnämnden i Göteborg

**Projekttitel:** Studie av invasiva hemolytiska streptokock grupp A infektioner i Västra Götalandsregionen under en 4-årsperiod

**Projekt ID:** iGAS-VGregion - 2013

**Version:** 01

**Beslutsprotokoll från sammanträde med Regionala etikprövningsnämnden i Göteborg, Medicinska avdelningen (M 2), den 23 september 2013**

**Föredragande:** Ulf Nilsson

**Sekreterarärende efter komplettering**

Nämnden, som uppfattar att det är VG-regionen och inte den projektansvarige som är forskningshuvudman, önskar dels att informationen till forskningspersonerna kompletteras med kontaktuppgifter till personuppgiftsombudet, dels att samtyckesformuläret separeras och förses med studietiteln som projektrubrik.

Regionala etikprövningsnämnden i Göteborg  
Box 401, 405 30 Göteborg  
Besöks- och leveransadress: Guldhedsgatan 5A, 413 20 Göteborg  
Tel: 031-786 68 21, 786 68 22, 786 68 23, Fax: 031-786 68 18  
[www.ebn.se](http://www.ebn.se)

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