EDITORIAL
Comment on CRISTAL study
L. Zafrani, C. Ince

ORIGINAL ARTICLE
Etomidate and S-ketamine for the intubation of patients on the intensive care unit

CASE REPORT
Heterogeneity in Streptococcus pyogenes infections in the ICU, a case series
M. Höhn, B. Speelberg
NVIC NAJAARSCONGRES

Donderdag 18 en vrijdag 19 september 2014

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Netherlands Journal of Critical Care
ISSN: 1569-3511
NVIC/® Domus Medica
P.O. Box 2124, 3500 GC Utrecht
T.: +31-(0)30-6868761

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In the Colloids Versus Crystalloids for the Resuscitation of the Critically Ill (CRISTAL) study, Annane and co-authors compared patients receiving crystalloids (n=1443) with those receiving colloids (n=1414) for acute hypovolemic shock in 57 intensive care units (ICU) in France, Belgium, North Africa, and Canada.1 Randomization was stratified by centre and by diagnosis (i.e. sepsis, multiple trauma and other causes of hypovolemic shock). Therapy in the trial was open label but outcome assessment was blinded to treatment assignment. For each patient the choice for either use of crystalloid or colloid was determined by randomization but the type of colloid or crystalloid used was left to the discretion of the clinician. In this design, in the crystalloid group the type of solution used was 86% isotonic saline, 18% Ringer’s lactate and 4% hypertonic saline; in the colloid group, 69% hydroxyethylstarch (HES), 6% albumin 4%, and 14% albumin 12%. Patients treated with colloids received less fluid than those treated with crystalloids. Mortality did not differ at day 28. However, patients treated with colloids had more days free of vasopressor therapy and mechanical ventilation at day 7 and day 28 and had a lower mortality at 90 days (30.7% in the colloids group versus 34.2% in the crystalloids group). No differences in the incidence of organ failure or renal replacement therapy were detected between the two groups.1

The choice of fluid resuscitation for patients in hypovolemic shock remains a highly controversial issue. In the Saline Versus Albumin Fluid Evaluation (SAFE) study, which included 6997 ICU patients, Finfer et al. did not find any difference in terms of outcomes at 28 days between patients resuscitated with either albumin 4% or normal saline.2 In 2008, in the VISEP trial (Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis), Brunkhorst et al. randomly assigned 537 patients with severe sepsis to receive either 10% pentastarch (200kD) or Ringer’s lactate for fluid resuscitation and found that starch was harmful, worsening renal outcomes and possibly increasing mortality.3 The Scandinavian Starch for Severe Sepsis/Septic Shock (6S) study that included 804 patients with severe sepsis, found that 130kD HES increased 90-day mortality and worsened acute kidney injury.4 The Crystalloid versus Hydroxyethyl (CHEST) trial reported a higher incidence of renal replacement therapy with HES compared to saline.5 In a recent study published in Critical Care in 2013, Meybohm et al. re-evaluated prospective randomized controlled trials that compared the effect of colloids with crystalloids in critically ill patients.6 They defined 6 major criteria needed for a trial to be taken into consideration providing valid evidence for the comparison between different fluid types. They proposed a 6-points score including short time interval from shock to randomization (<6 h), restricted use for initial volume resuscitation, use of any consistent algorithm for haemodynamic stabilization, reproducible indicators of hypovolemia, maximum dose of HES, and exclusion of patients with pre-existing renal failure or renal replacement therapy. If this score is applied to the CRISTAL study it scores a total of 5 points, whereas the VISEP, 6S and CHEST trial score respectively 2, 1 and 2 points.

The design of the CRISTAL trial is of particular interest for many reasons. First, patients had received no prior fluids for resuscitation during their ICU stay which may have been a considerable bias in many previous studies.3,4 In the CHEST and 6S trials, patients had already been resuscitated, were normotensive and arguably were not in need of the administered fluid regimens for the purpose of resuscitation. In this context one can question whether testing the effects of crystalloids to colloids in a blinded fashion is an appropriate study design. From this point of view, the CRISTAL is clinically more significant since it tests the efficacy in a clinical setting where fluids are indeed needed for resuscitation in a state of hypovolemia. Second, acute hypovolemia was confirmed at inclusion by hemodynamic parameters measurements (i.e. the combination of hypotension with evidence for low
filling pressures and low cardiac index as assessed either invasively or noninvasively and, signs of tissue hypoperfusion or hypoxia), assessing that these patients really needed fluid resuscitation. Indeed, adequate evidence of hypovolemia is of utmost importance in order to interpret data concerning the administration of colloids or crystalloids and may have been lacking previously. Third, the total dose of starches in the trial by Annane et al. never exceeded the dose recommended by regulatory agencies and they excluded patients with severe chronic renal failure, making the use of colloids (especially HES) safer. Indeed, in the CRISTAL trial, contrary to contemporary opinion on the effects of HES products based on the CHEST and 6S trial the use of these starches in the CRISTAL trial was not associated with renal dysfunction.

How can we integrate Annane et al.’s study into physiological data? From a physiological point of view, acute volume resuscitation with colloids should result in less amounts of fluids needed for hemodynamic stabilization compared to crystalloids. Moreover, one of the unwanted effects of fluids is the hemodilution-induced reduction of the oxygen carrying capacity of blood. In this regard, hematocrit would have been an easy an interesting parameter to look at. In a recent study, Konrad et al. compared in pigs the renal microvascular oxygenation effects by using either a crystalloid solution or an HES for acute normovolemic hemodilution to a fixed hematocrit of 15%. In their model, they found that more harm was inflicted on the kidney by the use of crystalloids than HES. In the future, we can expect that microcirculation measurements in humans may help to guide fluid resuscitation.

In contrast, colloid-induced acute kidney injury, with morphological lesions of the proximal tubular cells, or osmotic nephrosis has been reported after the infusion of low-molecular-weight dextran or HES, especially with the first generation products. The tubular lesions reflect the accumulation of proximal tubular lysosomes due to pinocytosis of exogenous osmotic solutes, for example, mannitol, sucrose, iodinated contrast media, or colloids. So how can we combine these contradictory data? First of all, if colloids are used, it is extremely important to use a colloid of any kind with due care, following recommended doses, as Annane and co-authors did in their study. HES should not be given to ICU patients for long periods of time with high cumulative doses. Second, third-generation iso-oncotic products appear to be safer when used correctly and should be preferred in the next clinical trials. If physiology cannot be a substitute for clinical data, a physiological approach is useful for addressing the issue because it can focus on mechanisms and deliver clarity regarding the disputed issues and provide guidance for the design of appropriate clinical trials.

As well as the major contribution of the results from the Annane et al. study, important caveats remain in the CRISTAL study. First, different types of colloids and crystalloids have been mixed in each group and side-effects can be different from one molecule to another. As mentioned above and due to potential harmful effects (especially to the kidneys) of hyperoncotic colloids, these should be ideally avoided. Second, as pointed out by authors, the differences in 90-day mortality rates between the two groups should be interpreted with caution. Indeed, 90-day mortality was a secondary outcome and the confidence intervals approach 1. Finally, if we go back to the 6-point score suggested by Meybohm et al., the CRISTAL study, as many other previous studies, lacks a standardized protocol and algorithm with predefined hemodynamic targets for fluid resuscitation and sequential reassessment of volume status after colloids or crystalloids have been administered.

In conclusion, the debate concerning colloids and crystalloids has not yet settled. The CRISTAL study adds a new milestone to the issue of fluid resuscitation but also raises new questions that will need to be answered in the next few years with appropriate and well-designed prospective studies.

References

Etomidate and S-ketamine for the intubation of patients on the intensive care unit: a prospective, open-label study

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Keywords – Etomidate, S-ketamine, intubation, intensive care unit, mortality

Abstract
Objective: We compared the mortality rate in patients administered a single dose of etomidate or S-ketamine for tracheal intubation during their stay on the intensive care unit.

Methods: A single centre prospective open-label study was performed. Intensive care patients with a diversity of diagnoses were included. For tracheal intubation, etomidate or S-ketamine were used; the primary endpoint was 28-day mortality. Length of stay, the usage of norepinephrine, and cortisol concentrations were secondary end points.

Results: A total of 322 patients with a mixture of diagnoses were initially included. After exclusions, 301 patients participated; 161 patients in the etomidate group and 140 patients in the S-ketamine group were analysed. The 28-day mortality of the etomidate patients was 38% and of the S-ketamine patients 39% (p=0.998). The length of stay was 16 days in the etomidate group and 19 days (p=0.318) in the S-ketamine group; the time of norepinephrine administration was 26 versus 29 hours (p=0.389) respectively. 24 and 48 hrs after administration of either drug, the cortisol levels had significantly decreased; there was no statistical difference between the etomidate and S-ketamine patients.

Conclusion: In contrast with a currently held opinion, the present study showed that the 28-day mortality after a single dose of etomidate or S-ketamine, administered to patients for tracheal intubation while on the intensive care did not differ.

Introduction
Infusion of etomidate in critically ill patients causes suppression of the cortisol production, which leads to an increase in mortality.1–3 Because of this, etomidate is no longer used for continuous sedation. However, despite the fact that a single dose of etomidate suppresses the cortisol production for up to 48 hours, etomidate is still used as an induction agent because of its hemodynamic stability.4–6 It remains unclear, however, if this has clinical consequences, despite the fact that several analyses have rejected etomidate as an induction agent.7,8 These reviews have to a large extent been based on retrospective studies in septic patients. In two prospective studies, in which etomidate was administered just before admission to the intensive care department, mortality was similar when compared with ketamine or midazolam.9,10 However, an induction agent is not only used at the start of critical illness, but also during the subsequent stay in the intensive care. In this situation, the patient’s condition can be quite different both with respect to the course of illness and the administration of several other drugs. We initiated a prospective study to compare the mortality in patients after either a single dose of etomidate or a single dose of S-ketamine administered on the ICU at any point during their stay.

Methods
Tracheal intubation in the intensive care is an emergency procedure, for which both etomidate and S-ketamine are registered drugs. As etomidate and S-ketamine were routinely used in our ICU, and because endotracheal intubation of intensive care patients is usually an emergency procedure, the Medical Ethics Committee approved the study with a waiver of informed consent (METC number 11-N-94).

The study was performed in a mixed, surgical and medical, adult ICU with 21 beds in a large teaching hospital from April 2008 until the end of 2009. The ICU consists of three equivalent units, staffed by the same medical staff. These units are not specialized and there is no difference in categories of patients. Etomidate and S-ketamine were common induction agents in all three ICUs. For the first ten months, etomidate (Etomidaat®
Lipuro, Braun, Melsungen, Germany) was the induction agent in two units, and S-ketamine (Ketanest-S®, Pfizer, Capelle a/d IJssel, the Netherlands) in the other unit. After ten months the agents were reversed. The medical staff was not involved in patient allocation to a particular unit. Nursing staff, responsible for patient allocation and not involved in the study, decided in which unit the patient would be admitted. Consequently, this is a cluster-randomized trial in which the chosen intensive care unit is the randomized element. All critically ill adult patients, who were intubated in one of the intensive care units, either shortly after admission or during their period of stay, were enrolled in the study. Patients with cerebral pathology were not excluded, because ketamine is deemed safe in these patients.11-13 Patients, who were already intubated before admission, did not participate; patients who had received etomidate less than 72 hours before were excluded. Etomidate was administered in a dose of 0.2–0.3 mg/kg bodyweight, and S-ketamine 0.5 mg/kg. In order to avoid unwanted psychological reactions, midazolam (Midazolam®, Actavis, Hafnarfjordur, Iceland) 2.5 mg, was added to the S-ketamine. For neuromuscular blocking, rocuronium (Rocuroniumbromide®, Fresenius Kabi, ’s Hertogenbosch, the Netherlands) was used; the use of opioids was left to the discretion of the attending intensivist. Corticosteroids were prescribed when necessary as clinical therapy and were not part of the study.

The primary end point was the mortality within 28 days after the administration of etomidate or S-ketamine. The patients were followed for 28 days, also if they were discharged from the intensive care during this period. Secondary outcomes were the length of stay (LOS) in the intensive care unit, and the use of norepinephrine, during the first 72 hours after administration of one of the study drugs. Immediately after intubation, and 24 and 48 hours later (t=0, t=24 hours, t=48 hours), blood was taken to determine the cortisol levels. The serum cortisol levels were determined by competitive immunoassay using a commercial kit (Advia Centaur, Siemens AG, Erlangen, Germany).

Table 1. Patient characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Etomidate (n=161)</th>
<th>S-ketamine (n=140)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean (sd)</td>
<td>66 (14)</td>
<td>67 (13)</td>
<td>0.523</td>
</tr>
<tr>
<td>Male/female</td>
<td>95/66</td>
<td>89/51</td>
<td>0.478</td>
</tr>
<tr>
<td>APACHE II</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (sd)</td>
<td>25 (7)</td>
<td>24 (7)</td>
<td>0.224</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>58</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td>13</td>
<td>14</td>
<td>0.858</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>25</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>65</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>Steroid patients*</td>
<td>59</td>
<td>61</td>
<td>0.269</td>
</tr>
</tbody>
</table>

*Patients treated with corticosteroids as clinical therapy

Statistical analysis
Prior to this study, the average mortality rate of mechanically ventilated patients on our intensive care unit was 35%. To exclude a 15% worse outcome in the etomidate patients with a one-sided α risk of 0.05 and power of 90%, at least 106 patients had to be included in each group. Mortality and other categorical data were compared with the Chi-square test. For age, APACHE score, cortisol levels, use of norepinephrine, and LOS the Student’s t-test was used.

Results
In total 322 patients were included. After exclusion of the patients who had received etomidate less than 72 hours before, a total of 301 patients – 161 receiving etomidate, and 140 receiving S-ketamine were included. Patient characteristics are presented in table 1, the outcomes in table 2. With respect to the characteristics, the groups were comparable, as were the number of patients treated with corticosteroids.

In this study, the 28-day mortality was the same after a single dose of etomidate or S-ketamine, administered in one of the ICUs. This result is contrary to the findings that a single dose of etomidate increases mortality, based on retrospective analyses of septic patient populations.14-16 In these retrospective studies, the use of etomidate was not randomized, and it is possible that, because of its hemodynamic stability, etomidate was just chosen for the most critically ill patients, resulting in a bias.7,17 In two prospective studies, comparing etomidate with ketamine or midazolam, mortality was found to be equal.9,10 Though Jabre’s study9 was performed in a series of patients with various diagnoses, patients were intubated outside the intensive care, before admission, while in the present study patients who had been intubated before admission to the ICU were excluded. Furthermore, in the present study, patients were included when intubation took place at any point during their stay on the ICU; therefore, the patients studied in our study are more likely to represent a cross-section of a general ICU adult population.

The equivalence of the secondary end points, LOS and treatment with norepinephrine, could mean that adrenal suppression is the same in both groups of patients, and indeed the cortisol results did not differ. Based on the reports that a single dose of etomidate suppresses cortisol production for up to 48 hours, blood samples were taken at intubation, and at 24 and 48 hours later. Diurnal cortisol rhythm was therefore
not taken into account. However, a diurnal rhythm seems to be absent in critically ill patients with different diagnoses, especially those with a longer stay.\textsuperscript{18} The cortisol levels were only included if all three measurements, at t=0, t=24 and t=48 hours, were performed. All three measurements of cortisol were performed in somewhat fewer than half the patients, due to the stir of daily clinical practice. This restricted inclusion means that the results from the patients who died within 48 hours were also omitted. The cortisol levels declined significantly in both groups. Exclusion of the cortisol results, if the set of three was not complete, could create doubts about the conclusion. Still, inclusion of all the cortisol results (not presented) led to the same result.

Although the decrease in cortisol levels after a single dose of etomidate is well known, the cortisol levels also decreased after S-ketamine. A negative influence on the adrenal function, caused by hypnotics other than etomidate, has previously been reported by Jabre et al.\textsuperscript{9} It was demonstrated that after a single dose of ketamine the reaction on the ACTH stimulation test is insufficient in 48% of patients. Sedation of critically ill patients with propofol or midazolam demonstrated a decrease in the cortisol level, although the response to the ACTH test was adequate.\textsuperscript{19} And an induction dose of thiopental reduced the response in the ACTH test in 29% of critically ill patients.\textsuperscript{20} It seems reasonable to conclude that the cortisol reduction found in these studies, and the reduction in both groups of the present study are probably the consequence of the critical illness and the induction of anaesthesia.

The mortality difference of 15%, which was the starting point of the study, can be criticized as a limitation. Although a 15% difference is important, a smaller difference would have been more relevant. However, in order to study this smaller difference a multicentre study will be necessary.

A number of patients were treated with corticosteroids and these therapeutic steroids can influence cortisol measurements.\textsuperscript{21} However, the use of hydrocortisone after a single dose of etomidate in patients who were not in septic shock does not influence the 28-day mortality.\textsuperscript{22} Because the number of the treated patients was comparable between the groups, one would expect the results to be influenced equally. Increased mortality following etomidate has been demonstrated in retrospective analyses of septic patients.\textsuperscript{14,16} Although the mentioned prospective studies, in patients with either various diagnoses or suspected sepsis, were not designed with mortality as a primary end point, the mortality outcomes are comparable to the present study.\textsuperscript{9,10} A shortcoming in large prospective studies studying sepsis is that on admission the diagnosis of sepsis is not always sure. For example, Tekwani et al. in their prospective study use the term ‘suspected sepsis’.\textsuperscript{10} In conclusion, the present study does not demonstrate a difference in 28-day mortality, after a single dose of etomidate or a single dose of S-ketamine, administered to critically ill patients with a diversity of primary diagnoses on the intensive care unit. Finally, the cortisol levels decrease after both the administration of etomidate and S-ketamine.

LOS: length of stay in the intensive care department, following intubation; if a patient died within 28 days, after discharge from the intensive care department, the patient was not included in the LOS group. Norepinephrine infusion during 72 hours after intubation. Cortisol concentrations, if all three specimen, t=0, 24 and 48 hours, were present. *p<0.01, **p<0.02 compared to t=0.

Table 2. Results.

<table>
<thead>
<tr>
<th></th>
<th>Etomidate (n=161)</th>
<th>S-ketamine (n=140)</th>
<th>P</th>
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<tbody>
<tr>
<td>Mortality</td>
<td>61 (38%)</td>
<td>54 (39%)</td>
<td>0.998</td>
</tr>
<tr>
<td>LOS days mean (sd)</td>
<td>16 (25)</td>
<td>19 (27)</td>
<td>0.318</td>
</tr>
<tr>
<td>Norepinephrine hours mean (sd)</td>
<td>26 (31)</td>
<td>29 (29)</td>
<td>0.389</td>
</tr>
<tr>
<td>Cortisol three specimen</td>
<td>n=64</td>
<td>n=73</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.67 (0.50)**</td>
<td>0.67 (0.50)**</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Trial registration: www.controlled-trials/ISRCTN39347168

We thank B Grimm, statistician, for his advice.

References

Nationale Kwaliteitsvisitatie
Intensive Care
Aanvraag visitatie 2014

Voor medische afdelingen en zeker ook intensive care afdelingen is het essentieel dat kwalitatief goede zorg wordt verleend.


Graag nodigen wij uw intensivecareafdeling uit om deel te nemen aan een kwaliteitsvisitatie in 2014. Voor beschikbare data en aanvullende informatie kunt u contact opnemen met het NVIC secretariaat via e-mail: secretariaat@nvic.nl, of per telefoon: 030-6868761.

Postnatal corticosteroids for the prevention of bronchopulmonary dysplasia

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Keywords – Bronchopulmonary dysplasia (BPD), postnatal corticosteroids

Abstract
Bronchopulmonary dysplasia (BPD) remains a common complication of preterm birth with long term substantial consequences. The administration of postnatal corticosteroids in an attempt to attenuate the chronic lung injury is still a matter of ongoing debate after more than 30 years of research. Systematic reviews of the available randomised controlled trials (RCTs) have shown that administration of the main investigated corticosteroid, dexamethasone, is beneficial for short term pulmonary morbidity and mortality, but concerns about long term neurodevelopmental sequelae have resulted in recommendations of restricted use. Although these systematic reviews pool the results of the RCTs as they were homogeneous, they are hampered by clinical heterogeneity in terms of investigated cumulative dosage regimens. In this review, we will discuss the clinical consequences of the changes in prescribing postnatal steroids in this high risk population and provide new evidence on the modulating effects of the heterogeneity within the trials. Finally, we will discuss alternative strategies for the administration, the subtypes of postnatal corticosteroids and future research perspectives.

Introduction
Bronchopulmonary dysplasia
The implementation of antenatal glucocorticoids, postnatal surfactant therapy, new modalities of respiratory support and nutritional intervention in perinatal and neonatal care have led to increased survival in the lowest birth weight infants. However, this improved survival is associated with high rates of short term morbidities and long term neurodevelopmental sequelae, of which bronchopulmonary dysplasia (BPD) continues to be the most important complication.12 Despite the above advances in neonatal care, the prevalence of BPD has shifted little, although both the etiology and clinical picture of BPD have changed over recent decades.

Incidence and health burden of BPD
In the Netherlands, less than one percent of live born infants are born with a gestational age under 30 weeks and/or a birth weight less than 1250 g, resulting in more than 1000 of these preterm infants at the highest risk of developing BPD each year.13,14 Unfortunately, exact data on the incidence of BPD in the Netherlands are lacking, but published international cohort studies show incidences of approximately 23% in infants born at 28 weeks, increasing to 73% in infants born at 23 weeks.1,15 BPD is characterized by extended respiratory support, a compromised lung function during a prolonged primary hospitalization for several months and recurrent respiratory infections during the first years of life, as well as long term...
pulmonary morbidity into adolescence.\textsuperscript{16-19} Furthermore, and of even more importance, patients with established BPD are at high risk of cerebral palsy (CP) and developmental delay as BPD has repeatedly been shown to be an independent risk factor for adverse neurodevelopmental outcome with a high correlation between these adverse outcomes and the severity of the condition.\textsuperscript{12,20-22}

BPD is considered a multifactorial disease, where as well as genetic susceptibility, intrauterine growth restriction, nutritional deficits, direct mechanical injury caused by artificial ventilation, oxygen toxicity and pulmonary inflammation have been identified as important causes of its development, thus explaining the rationale of using antenatal and postnatal corticosteroids (figure 1).\textsuperscript{5,6,23,24}

Evidence for postnatal corticosteroid therapy

Pulmonary inflammation plays a central, modulating role in the pathogenesis of BPD and glucocorticoids have a strong anti-inflammatory effect, making them an ideal candidate for attenuating the inflammatory response associated with BPD: the rationale of glucocorticoids seems justified. However, after 30 years of research, the administration of corticosteroids for the prevention and treatment of BPD in preterm infants is still one of the most controversial and ongoing hot topics in neonatology.

International recommendations

In the mid 1990s RCTs clearly showed that systemic corticosteroids, mainly dexamethasone, significantly reduced the incidence of BPD and the combined outcome BPD and death, in preterm infants at risk.\textsuperscript{25,26} Systematic reviews including all these RCTs divided the therapy according to the timing of starting administration, being early (<96 hr), moderately early (7-14 days) or late (>3 weeks) onset.\textsuperscript{27-29} All these reviews showed a significant reduction in the combined outcome mortality and BPD at 28 days postnatal age and 36 weeks PMA in the group of patients receiving systemic corticosteroids compared to placebo, regardless of the timing of administration. Furthermore, the treated infants could be extubated earlier. However, these beneficial effects were at the cost of short term transient adverse effects, such as hyperglycemia, gastrointestinal bleeding, gastrointestinal perforation and hypertension.

This led to the belief that glucocorticoids could be the “magic bullet” for the treatment of preterm infants at high risk of BPD. As a consequence, 25-50% of all extreme preterm infants were treated with glucocorticoids in the late 1990s.\textsuperscript{30,31} However, the international view on postnatal corticosteroids changed after the publication of the first reports on long term neurodevelopmental outcome into a stigma of “misguided rockets” for these trials showed an association with increased risk of abnormal neurological development.\textsuperscript{32,33} The results of the systematic reviews divided by the timing of administration were not as consistent on this outcome as they were on the beneficial pulmonary outcome.\textsuperscript{34,35} The meta-analysis of trials investigating glucocorticoid therapy at an early onset showed a significant increase in adverse long term neurological development, such as cerebral palsy (CP), neurological exams and developmental delay.\textsuperscript{34} In contrast, the reviews on moderately early and late administration (>seventh day of life) did not show any difference between the treated patients and the placebo group.\textsuperscript{35}

In response to these reports, the American Academy of Pediatrics, the Canadian Pediatric Society and the European Association of Perinatal Medicine, concluded that routine use of systemic dexamethasone in the treatment of BPD could no longer be recommended until further research had established the optimal type, dose and timing of corticosteroid therapy.\textsuperscript{36,37} Furthermore, this recommendation was recently affirmed in a publication stating that current evidence is insufficient to recommend other corticosteroid doses and preparations.\textsuperscript{38}

Changes in BPD incidence

The international neonatal community has discarded the use of early postnatal glucocorticoids completely for the above reasons and is therefore not a subject for this review. Regarding the use of moderately early or late postnatal systemic glucocorticoids, clinicians encounter a dilemma facing those
patients at high risk of BPD, since BPD is associated with an increased risk of adverse neurological outcome itself.\textsuperscript{12} The debate is still ongoing that BPD is a direct cause of adverse long term neurological outcome or an indirect sign of increased systemic inflammatory status leading to that adverse outcome. A systematic review using meta-regression showed that the adverse effects of moderately early or late administrated postnatal glucocorticoids on long term neurodevelopmental outcome might be modified by the BPD risk.\textsuperscript{20} However, in line with the current opinion of postnatal corticosteroids being “misguided rockets”, clinicians postpone its administration until the third to fourth week of postnatal life, lowering the dosage schedule of dexamethasone or changing to alternative corticosteroids without knowing the effect of this policy change on the benefit to risk ratio.

Several cohort studies have been performed including cohorts of high risk preterm infants divided in periods before and after the published international recommendations on the restricted use of postnatal corticosteroids.\textsuperscript{40-42} These studies showed that with a decline in the use of postnatal corticosteroids, the incidence of BPD increased. Furthermore, approximately ten percent of preterm infants are still being treated with this therapy, where the clinician faces the dilemma on which treatment, with what cumulative dose (daily dose times duration of therapy) or duration itself, the patient will have the optimum benefit to risk ratio.\textsuperscript{30} 

**New insights**

**Lowering the dose: head-to-head comparison**

In order to determine what the effects are of lowering the cumulative dose of dexamethasone to minimize the adverse effects, we first performed a systematic review, of all RCTs comparing head-to-head a higher versus a lower dosage regimen of dexamethasone in ventilated preterm infants.\textsuperscript{43} Patients who participated in these trials received steroids so that these were not placebo controlled trials. Six studies enrolling a total of 209 participants were included; two studies contrasted the cumulative dexamethasone dose in the higher ranges (>2.7 mg/kg in the higher dose regimen) and four in the lower ranges (≤2.7 mg/kg in the higher dose regimen). Meta-analysis revealed no effect of dexamethasone dose on mortality and neurodevelopmental sequelae in these two subgroups. Subgroup analysis of the studies contrasting the dexamethasone dose in the higher ranges showed that the highest dose of dexamethasone was more effective in reducing BPD than the lower dose (typical relative risk (TRR) 0.67; 95% confidence interval (CI) 0.45, 0.99; figure 2). These data suggested that a reduction in dexamethasone dose might increase the incidence of BPD without decreasing the risk for adverse neurodevelopmental outcome. However, the validity of this observation is compromised by the small sample of randomised children, heterogeneity on study populations and designs, the use of late rescue corticosteroids and the lack of long term neurodevelopmental data in some studies.\textsuperscript{43}

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**Figure 2.** Meta-analysis of the combined outcome death and BPD at PMA of 36 weeks. High-range contrast indicates trials using cumulative dexamethasone doses in the higher ranges (≥ 2.7 mg/kg in the higher-dosage regimen). Low-range contrast indicates trials using cumulative dexamethasone doses in the lower ranges (≤2.7 mg/kg in the higher-dosage regimen). Each dot is relative risk (RR) of one study. The size of the shaded square indicates the weight of the study in the meta-analysis. The horizontal line indicates the 95% confidence interval (CI). The diamond indicates the subtotal of the studies shown above (meta-analysis), the centre being the typical RR and the distance between the extremes (left and right) being the 95% CI. The arrow in the study by Ramanathan et al.\textsuperscript{59} indicates that the 95% CI exceeds the scaling of the RR shown at the bottom. The vertical line indicates a RR of one (no difference).
Lowering the dose: revisiting the placebo controlled RCTs

To further determine the effects of lowering the dexamethasone, we re-analyzed the known placebo controlled dexamethasone trials initiating therapy after the first week of life. The known reviews stacked information from trials with tremendous clinical heterogeneity in their cumulative dose and duration of therapy, and timing of therapy onset. Using this clinical heterogeneity, we divided the different RCTs into subgroups and performed meta-regression according to the used cumulative dexamethasone dose to determine the effect modification of these variables.

This systematic review included sixteen trials randomising 1,136 patients. Trials with a moderately early (7-14 days) or delayed (>3 weeks) postnatal treatment onset were analyzed separately. Meta-analyses of the subgroup showed that higher dexamethasone doses reduced the TRR for the combined outcome mortality or bronchopulmonary dysplasia, with the largest effect in trials using a cumulative dose above 4 mg/kg (moderately early TRR 0.57; 95% CI 0.39,0.84; delayed TRR 0.75; 95% CI 0.60,0.93; figure 3). No effect was found of doses on the risk of neurodevelopmental sequelae in the delayed treatment studies, but in the moderately early treatment studies the risk of mortality or cerebral palsy decreased by 6.2% (95% CI -11.1%,-1.3%), and the risk of a mental developmental index below -2SD decreased by 6.6% (95% CI -13.0,-0.2) for each incremental mg/kg cumulative dexamethasone dose (figure 4). Higher cumulative dexamethasone doses administered after the first week of life may decrease the risk for BPD without increasing the risk for neurodevelopmental sequelae in ventilated preterm infants. Even more striking was the finding that in the moderately early treatment studies, the risk of neurodevelopmental sequelae was decreased for each incremental mg/kg cumulative dexamethasone dose.

At present we can only speculate on the possible mechanisms for this time dependent effect of dexamethasone therapy on neurodevelopmental outcome. First, as suggested by animal data, the direct effect (beneficial or harmful) of dexamethasone on the brain might differ depending on the postnatal age of exposure. Second, the effect of dexamethasone on the pulmonary condition and outcome (i.e. BPD), may also indirectly affect neurodevelopmental outcome. Protracted mechanical ventilation has been shown to be an independent risk factor for neurodevelopmental sequelae. As starting dexamethasone in the moderately early time frame will almost certainly reduce the time on mechanical ventilation compared to delayed treatment, it may thus reduce the risk for CP. A recent study in preterm baboons showed that a difference as small as five days of mechanical ventilation already results

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**Figure 3.** Overall and subgroup meta-analysis of the combined outcome mortality or BPD at 36 weeks PMA in the moderately early treatment studies. CD indicates cumulative dosage. A) Cummings et al. dexamethasone arm with cumulative a dose of 3.0 mg/kg versus placebo; B) Cummings et al. dexamethasone arm with a cumulative dose of 7.8 mg/kg versus placebo.

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
<th>Treatment</th>
<th>Control</th>
<th>Weight %</th>
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<tr>
<td>CD &lt;2.0 mg/kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kovacs</td>
<td>0.95 (0.64, 1.41)</td>
<td>18/30</td>
<td>19/30</td>
<td>21.05</td>
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<tr>
<td>Walter</td>
<td>0.67 (0.31, 1.45)</td>
<td>6/17</td>
<td>10/19</td>
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<tr>
<td>Subtotal (I-squared=0.0%, p=0.426)</td>
<td>0.86 (0.60, 1.23)</td>
<td>24/47</td>
<td>29/49</td>
<td>31.52</td>
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<tr>
<td>CD ≥2.0 mg/kg and &lt;4.0 mg/kg</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cummings (a)</td>
<td>0.92 (0.73, 1.16)</td>
<td>11/12</td>
<td>11/11</td>
<td>13.25</td>
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<tr>
<td>Durand</td>
<td>0.32 (0.12, 0.84)</td>
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<td>Kari</td>
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<td>7/12</td>
<td>7.42</td>
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<tr>
<td>Vento</td>
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<td>8/10</td>
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<tr>
<td>Subtotal (I-squared=74.7%, p=0.008)</td>
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<td>26/56</td>
<td>37/53</td>
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<tr>
<td>CD ≥4.0 mg/kg</td>
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<tr>
<td>Cummings (b)</td>
<td>0.63 (0.41, 0.98)</td>
<td>8/13</td>
<td>11/11</td>
<td>13.72</td>
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<tr>
<td>Romagnoli</td>
<td>0.45 (0.21, 0.99)</td>
<td>5/15</td>
<td>11/15</td>
<td>12.19</td>
</tr>
<tr>
<td>Subtotal (I-squared=0.0%, p=0.425)</td>
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<td>13/28</td>
<td>22/26</td>
<td>25.91</td>
</tr>
<tr>
<td>Overall (I-squared=50.4%, p=0.049)</td>
<td>0.70 (0.57, 0.86)</td>
<td>63/131</td>
<td>88/128</td>
<td>100.00</td>
</tr>
</tbody>
</table>

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Favours dexamethasone Favours placebo
In a decreased brain growth and the presence of subtle brain injury.\textsuperscript{46}

In addition to mechanical ventilation, BPD itself is an important independent risk factor for CP.\textsuperscript{47} Therefore, reducing the incidence of BPD, when starting dexamethasone treatment moderately early, might, in part, explain the time dependent (moderately early vs delayed) effect of dexamethasone on CP. Considering these mechanisms in combination, it might well be that a direct negative effect of dexamethasone on the brain is overridden by the indirect beneficial effect mediated via a reduction in time on mechanical ventilation and the incidence of BPD.

Alternative administration corticosteroid therapy

Given the above mentioned concerns on adverse neurodevelopmental sequelae with systemic administration of corticosteroids, local administration via the inhalation route might be an effective and safe alternative. However, the updated Cochrane review, which identified eight RCTs initiating therapy ≥ seventh day of life, randomising 232 preterm infants showed a paucity of data on short term and long term adverse effects, and furthermore, the included trials differed considerably in patient characteristics, inhalation therapy and outcome definitions.\textsuperscript{48} The sparse meta-analyses that could be done showed that inhaled glucocorticoids did not reduce the separate or combined outcomes of death or BPD, or have beneficial effects on short term respiratory outcomes such as failure to extubate and total duration of mechanical ventilation or oxygen dependency, although there was a trend to a reduced use of systemic glucocorticoids in favour of inhalation corticosteroids. Based on these results the use of inhalation glucocorticoids initiated at ≥7 days of life for preterm infants at high risk of developing BPD cannot be recommended at this point in time.\textsuperscript{46}

Alternative type of corticosteroids

The same concerns for the long term neurodevelopmental outcomes for administering dexamethasone have led to the introduction of alternative anti-inflammatory corticosteroids, such as hydrocortisone. Animal studies have suggested that, in contrast to dexamethasone, hydrocortisone has no detrimental effect on the brain.\textsuperscript{49} Historical cohort studies have suggested that hydrocortisone treatment is equally effective in reducing death or BPD compared with infants treated with dexamethasone without causing an increased risk of adverse neurological outcome.\textsuperscript{50,51,52,53}

To date, eight RCTs including 880 infants have investigated a low hydrocortisone dose started within <72 hours after birth (early treatment onset) without a clear reduction in the incidence of death or BPD.\textsuperscript{54} Only one of these trials reported long term follow-up, showing no differences in adverse neurodevelopmental sequelae.\textsuperscript{55}

No placebo controlled randomised trials have investigated the use of hydrocortisone after the first week in life in ventilator-dependent preterm infants. However, more and more NICUs in the Netherlands are switching from using dexamethasone to hydrocortisone, despite the lack of evidence that hydrocortisone is effective and safe. For that reason, the SToP-BPD trial was designed and is currently recruiting.\textsuperscript{56}

It is a randomised double blind placebo controlled study in preterm infants, who are ventilator-dependent at a postnatal age of 7-14 days and have a suspected diagnosis of developing BPD. Compared to the early RCTs using a low dosage regimen, the investigated regimen of hydrocortisone has a cumulative dose 72.5 mg/kg and will be administered during a 22 day tapering schedule. Randomising patients into placebo seems justified, since at a global level, neonatologists are not willing to initiate steroids in the second week of life, but only as a rescue therapy in the third or fourth week of life. At the end of 2015 this trial will have determined the role of postnatal hydrocortisone administration at a moderately early onset in ventilator-dependent preterm infants.

Future perspectives based on current evidence

The cohort studies showing an increase of BPD incidence with the decreasing use of postnatal corticosteroids, the findings of the above-mentioned head-to-head comparison of a higher versus lower dosage regimen, as well as the subgroup and meta-regression analyses of the placebo controlled trials all
suggest that the current recommendations of lowering the dose and the duration of postnatal corticosteroids might not be in the best interest of preterm infants at high risk of BPD. However, we would like to emphasize that these underpowered or indirect suggestions of evidence should be confirmed in randomised controlled trials.

A large multicenter study, comparing a higher cumulative dexamethasone dose (≥4 mg/kg) with a lower dose (≤2 mg/kg) using a comparable duration of treatment at moderately early onset, is urgently needed. The clinical community should decide if there is still room for a placebo arm in such a trial. Such a trial should be adequately powered to detect small but clinically relevant treatment effects. Dilution of treatment effect due to the use of corticosteroids outside the study protocol, or crossing over between trial arms should be avoided as much as possible. Data should be analyzed on an intention-to-treat basis, per-protocol, and in an adherers-only analysis in order to accurately estimate the true effect of dexamethasone treatment on the clinical outcome parameters.

Second, future research should focus on the optimal aerosol delivery system for the administration of inhaled glucocorticoids in ventilated and non-ventilated infants, which is quite a challenge since preterm infants have low tidal volumes and functional residual capacity, high respiratory rates, a shortened particle residence time and in general smaller airway diameters. A large RCT administrating inhaled corticosteroids at an early onset is currently recruiting patients, whereas in the Netherlands and Belgium the SToP-BPD trial will provide data on the use of hydrocortisone at a moderately early onset in the near future.

Conclusions

These new systematic reviews on postnatal corticosteroids using subgroup meta-analyses and meta-regression show that the current practice of lowering the cumulative dose of dexamethasone in preterm infants does not result in a better benefit to risk ratio, but instead diminishes the positive effects on the incidence of the combined outcome death or BPD without lowering the adverse neurodevelopmental sequelae. Furthermore, it confirms that the optimal timing of therapy onset is between seven and fourteen days of postnatal life. Finally, we show that there is no evidence to support the use of the alternative method of administration (i.e. inhalation glucocorticoids) or alternative drugs, namely hydrocortisone to prevent the development of BPD in high risk preterm infants.

References


Abstract
Lactic acidosis type B is a rare complication in patients with haematological malignancies. This article reports a single patient case with lactic acidosis as a first presentation of acute myeloid leukaemia. Finally, we briefly speculate on the pathogenesis of this disorder.

Introduction
Developing type B lactic acidosis (LAB) in the setting of a haematological malignancy is a rare complication with poor outcome. LAB in haematological malignancies has a multifunctional aetiology. We report a case of an 82-year-old woman who presented with LAB as the first presentation of acute myeloid leukaemia.

Case report
An 82-year-old woman was referred to the emergency department of the Amphia hospital Breda because of acute progressive shortness of breath and no response to antibiotic treatment and prednisone. Her medical history mentioned no respiratory or cardiac disease and no diabetes or use of drugs. On admission the patient was tachypnoeic with a decreased level of consciousness and normal blood pressure. Physical examination revealed no evident cause for respiratory insufficiency. Chest X-ray and electrocardiography were normal. Arterial blood gas analysis showed: pH 7.03, PCO 7.6 kPa, PO 12.4 kPa, bicarbonate 15.0 mmol/L and a base excess of -15.4 mmol/L. Plasma level of lactic acid was 12.4 mmol/L. Serum creatinine was 84 µmol/L. The full blood count showed anaemia (Hb 4.6 mmol/L), thrombopenia of 32x10^9/L and leukocytosis of 280x10^9/L, with a differential count of mainly myeloblasts indicating acute myeloid leukaemia (AML). Despite respiratory support with intubation and mechanical ventilation after admission to the intensive care unit, our patient deteriorated and died the same day. No medication was given because of her poor prognosis.

Discussion
Lactic acidosis (blood lactate concentration >5mmol/L and pH <7.30) is the most common cause of metabolic acidosis. Lactic acid is the normal endpoint of the anaerobic breakdown of glucose in the tissues and is transported to the liver when it exits the cells. In the liver, lactic acid is oxidized back to glucose. In the setting of decreased tissue oxygenation, lactic acid is produced as the anaerobic cycle is utilized for energy production. Lactate is cleared from the blood primarily by the liver and to a smaller degree by the kidneys and skeletal muscles. Under normal circumstances the body produces 15-20 mmol/kg lactic acid per 24 hours.

Malignant cells can switch their metabolism towards the glycolytic pathway despite normal oxygen concentrations leading to excessive lactic acid production (Warburg effect) which is normally counterbalanced by the gluconeogenesis in the liver. This metabolic balance can be disrupted and end up as LAB. An increase in the glycolytic rate in tumour cells can be due to an aberrant insulin-like growth factor (IGF) signalling system that induces overexpression of hexokinase type II, a rate-limiting enzyme involved in glucose consumption by the cell. Other mechanisms described that result in LAB, are an increase in lactate production by the action of tumour necrosis factor-alpha, and cytokine involved in systemic inflammation by reducing the activity of pyruvate dehydrogenase. Thiamine deficiency has been suggested because thiamine is...
an important co-factor for converting pyruvate into acetyl coenzyme A in the Krebs Cycle and without this conversion, anaerobic metabolism will prevail.1

Tumour microembolism can also cause lactic acidosis, or decreased hepatic clearance of lactic acid due to extensive liver involvement.2 However, many case reports in the literature show no evidence of liver infiltration.2,6 In addition, no evidence has been found for extensive liver metastasis as a cause for LAB.2 LAB in (haematological) malignancy indicates a poor and often fatal outcome and can be considered as a marker of poor prognosis regardless of treatment. Even improvement of disease activity as a result of response to chemotherapy is generally temporary. Aggressive chemotherapy has been effective in a small group of patients and is still the first choice of treatment. Alkalinization seems to be a logical choice but seems ineffective.1 Administered bicarbonate is immediately converted to CO2 and if the patient is unable to eliminate the additional CO2 by increased ventilation the pH will not change.1,2,3

The cause of respiratory distress in our patient is probably due to the obstruction of the pulmonary vasculature caused by leukostasis or by extensive tumour emboli at the time of clinical manifestation of her leukaemia. She also presented with lactic acidosis which carries a very poor prognosis. At this age chemotherapy is not an option, since it would only give a temporary improvement as the literature states.

**Conclusion**

The metabolic imbalance between excessive production of lactic acid by malignant cells and hepatic lactic acid utilization causes lactic acidosis type B. However, the exact pathogenesis of this mechanism in malignancies is still poorly understood.1-6 The literature states an unfavourable prognosis of LAB in haematological malignancies. Chemotherapy is generally only a temporary successful treatment.

As caregiver one should be aware of the poor prognosis of LAB and be cautious with overtreatment.

**References**

CASE REPORT

“Double arrest” - Amphetamine fatality in a 31-year-old male: a case report

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Keywords – Amphetamine, intoxication, cardiotoxicity

Abstract
Amphetamine abuse in the general population in the Netherlands is relatively limited and stable. Approximately 0.2% of the Dutch population used amphetamine in 2005. Fatal cases of amphetamine-associated cardiotoxicity (myocardial infarction or necrosis, acute cardiac failure or cardiac arrhythmia) are rarely reported in medical literature.

This report describes the case of a 31-year-old male standing in front of his bedroom window, swinging an axe and threatening to jump. During a struggle with the police in which pepper spray was used, the patient suddenly collapsed and lost consciousness. Police officers immediately started with basic life support. After twenty-one minutes of resuscitation there was a sinus tachycardia and output. The evening prior to his struggle with the police, the patient had smoked 1.5 gram of speed.

Toxicological analysis in the patient's urine revealed a concentration of 26 mg/L of amphetamine (toxicological level >0.2 mg/L) and 18 μg/L of methamphetamine (toxicological level >0.2 mg/L). No traces of pepper spray were found. Initial electrocardiogram revealed diffuse ischemia. On our ICU, refractory cardiogenic shock developed and was eventually followed by death, approximately 30 hours after admission.

Introduction
Amphetamine abuse in the general population in the Netherlands is relatively limited and stable. Approximately 0.2% of the Dutch population used amphetamine in 2005.¹ Amphetamine-associated cardiotoxicity (myocardial infarction or necrosis, cardiomyopathy, and cardiac arrhythmia) cases are rarely reported in medical literature.

We describe a case of sudden cardiac arrest after amphetamine abuse, followed by refractory cardiogenic shock and eventually death.

Case
A 31-year-old male was observed by neighbours standing in front of his bedroom window on the first floor shouting, threatening to jump and swinging an axe. Neighbours called in the emergency services. Police officers forced the door and tried to arrest the male. Pepper spray and physical force were used to overwhelm him. During the struggle, he suddenly collapsed and lost consciousness. Police officers immediately started basic life support. Seven minutes later, a team of paramedics arrived on the scene. The first heart rhythm found was asystole. After twenty-one minutes of resuscitation, and after the administration of 5 mg adrenaline and 3 mg atropine, the patient had a sinus tachycardia and cardiac output. After this successful resuscitation he was transported to the emergency department of our hospital.

On arrival at our emergency department, the patient's vital signs were: blood pressure 80/40 mm Hg, heart rate 120/minute, SpO2 97%, temperature 36.4° C and Glasgow Coma Scale score E1 M1 V tube. His pupils were dilated and did not respond to light. Heart and lung sounds were normal and the abdomen showed no abnormalities. The patient's right wrist and left tibia were extensively bruised. Initial ECG showed diffuse ischemia and chest X-ray showed no pulmonary pathology, however, the heart appeared to be enlarged (figure 1).

Routine laboratory investigations were performed: arterial blood gas measurements showed a severe metabolic acidosis (table 1).

At that time it remained unclear on what grounds sudden cardiac arrest had occurred. Taken into account the young age and the circumstances in which the sudden cardiac arrest had occurred, blood and urine samples were obtained for toxicological analysis. Because it was unclear at the time what the origin of the sudden cardiac arrest and the first presented rhythm were, we decided to start a 24 hours hypothermia protocol.²,³ During the hypothermia protocol, the patient showed persisting hypotension, so fluid resuscitation and noradrenalin were started.

Four hours after admission to the ICU, hetero-anamnesis revealed that the patient used speed on a regular basis. He started to smoke speed at the age of fifteen and was not a daily user, but
used three to four times per month. Quantity of this usage could not be specified by his family. His girlfriend admitted that on this occasion he had smoked 1.5 gram of speed.

Toxicological screening of his urine was positive for amphetamine, and quantitative analysis showed a concentration of 26 mg/L of amphetamine (toxicological level >0.2 mg/L) and 18 ţgr/L of methamphetamine (toxicological level >0.2 mg/L). No traces of the contents of pepper spray (capsaicine, dihydrocapsaicine or nordihydrocapsaicine) were found.

During admission to the ICU the patient developed a severe rhabdomyolysis (table 1). Creatinekinase rose to a maximum of 10,440 U/L. For renal protection, forced diuresis was started with an infusion of sodium bicarbonate at a concentration of 1.4% at a rate of 4 litres per 24 hours.

Thirteen hours after admission the patient became haemodynamically instable, with a blood pressure of 60/40 mm Hg. The shock was unresponsive to fluid resuscitation and noradrenalin up to a rate of 0.6 microgram/kg/min. It was therefore necessary to terminate the 24 hours hypothermia protocol. One hour later, the patient appeared more and more dependent on inotropic drugs. Therefore, it was decided to add adrenalin at a rate of 0.2 microgram/kg/min and phenylephrine at a rate of 1 mg/hour. Despite changes in ventilator settings and an infusion of sodium bicarbonate, the patient became more and more acidotic. The patient remained haemodynamically unstable, and did not respond to gradually increased adrenalin up to a rate of 1.2 microgram/kg/min. Fluid resuscitation with colloids

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**Table 1.** Laboratory results.

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<th></th>
<th>ER</th>
<th>1.5 h</th>
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<td>3.2</td>
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did not have any effect. At this point, the patient’s blood pressure dropped to 55/35 mm Hg and could not be raised either by increasing the inotropic drugs or fluid resuscitation with colloids. Despite all these efforts the patient died as a consequence of cardiac failure.

**Discussion**

Our patient sustained a sudden cardiac arrest after amphetamine abuse. Amphetamines are a class of noncatechol sympathicomimetic amines that produce central nervous stimulation. Amphetamines induce euphoria, increase alertness, intensify emotions and boost self-esteem. Because of these effects amphetamines are a popular party drug. A research study conducted among visitors of bars and cafes in Amsterdam showed that 17 percent of the visitors had experience with amphetamine.

In excessive doses amphetamines cause anxiety, hallucinations, coma, seizures, cardiotoxicity and agitation. Amphetamines can be used orally, per inhalation, and intravenously. After inhalation, amphetamine has a strong and direct effect. Amphetamines are metabolized in the liver. Twenty to 65% of amphetamines are eliminated through the kidneys in unchanged form, and the remaining percentage is excreted as metabolites. Physical half-life is 10-30 hours in normal urine, but is strongly prolonged in alkaline urine (up to 140 hours).

To date, reports about amphetamine-associated cardiotoxicity remain scarce.

Cardiotoxicity of amphetamine and its synthetic derivates can manifest itself as: acute myocardial infarction or necrosis, arrhythmias, cardiomyopathy and acute heart failure. There is a number of possibilities that could have induced the sudden cardiac arrest in this case. Firstly, amphetamine is an indirectly acting sympathicomimetic that stimulates the release of noradrenaline from sympathetic nerves. This release of noradrenaline has a pressor effect on the coronary arteries. Also, amphetamine can induce myocardial necrosis. For example, it has been demonstrated in rats that administration of methamphetamine results in the loss of myoglobin in the ventricular myocardium, swelling and degeneration of myochondria in affected myocytes, sarcocemmal damage, myocytolysis and fibrosis. Thirdly, it has been described that amphetamine can induce acute as well as chronic cardiomyopathy.

It is known that patients placed in physical restraints can suffer sudden cardiac arrest due to a combination of dehydration, adrenergic neurotransmitters, and metabolic acidosis. Heavy muscle contraction during the struggle most certainly contributed to the rise in creatinine kinase and also the severe (lactate) acidosis.

Autopsy showed an 80% stenosis of the left anterior descending artery, and a 50% stenosis of the left circumflex coronary artery. No valve vitia were found. The weight of the heart was 430 gram. Macroscopically, there were multiple infarctions visible in the lateral and inferior wall of the left ventricle, with a maximal diameter of 0.5 cm x 0.5 cm. Microscopic LDH colouring showed a concentric decolouring of the left ventricle. It is difficult to establish which of the above described mechanisms led to the sudden cardiac arrest in our patient. Most likely it was a combination of pathophysiological mechanisms and, in his agitated state, coronary vascular spasm could have led to diffuse infarction. Possibly, infarction was speeded up as a consequence of increased oxygen demand, caused by the struggle with the police. Also the pre-existent coronary artery stenosis in two coronary arteries may have speeded up the infarction. Massive efflux of potassium, caused by diffuse infarction could have led to an arrhythmia.

The irritating substances in pepper spray used by the Dutch police are capsaicin, dihydrocapsaicin and nordihydrocapsaicin. No traces of these substances were found at toxicological analysis. However, the use of pepper spray on our patient could have induced the feeling that breathing was impossible. Combined with the physical struggle this could have led to a decreased availability of oxygen to the myocardium.

In conclusion, amphetamine can cause cardiotoxicity in different ways. In our patient, amphetamine intake together with physical exertion most likely caused diffuse coronary vascular spasms, resulting in diffuse infarction and eventually arrhythmia.

**References**


NVIC CURSUSSEN LUCHTWEGMANAGEMENT OP DE IC

Woensdag 4 en donderdag 5 juni 2014
Maandag 17 en dinsdag 18 november 2014

LOCATIE: Hotel Houten en Skillscenter OSG te Houten

Luchtwegmanagement
Luchtwegmanagement is een van de belangrijkste taken van de intensivist. Regelmatig zijn spoedintubaties noodzakelijk. Vaak is sprake van gecombineerde problematiek, is er minder tijd en zijn de omstandigheden minder gunstig dan in electieve situaties. Dit vereist een brede aanpak met aandacht voor oxygenatie, circulatie en medicatie.

Opzet van de tweedaagse cursus
De tweedaagse NVIC Cursus Luchtwegmanagement op de IC is een intensieve en praktijkgerichte cursus. In kleine groepen worden verschillende luchtwegtechnieken geoefend en diverse scenariotrainingen gedaan. Aan de hand van ingestuurde casuïstiek wordt ruim aandacht besteed aan luchtwegstrategieën.

Aanvullende informatie en inschrijven via www.nvic.nl.
**Abstract**

*Streptococcus pyogenes* can cause severe invasive infections with a broad spectrum of clinical presentations. When not diagnosed and treated in time, the course of this infection can be fatal. We illustrate the different clinical presentations by presenting three manifestations of group A beta-haemolytic *Streptococcus* infections; a 45-year old woman with severe toxic shock like syndrome with a dramatically rapid course and fatal outcome, a 35-year old woman with *Streptococcus pyogenes* meningitis, which is highly unusual, and a 73-year old man with erysipelas caused by *Streptococcus pyogenes* and subsequent septic shock. New insights have been gained regarding virulence factors within both host and pathogen that play a crucial role in the differences in pathogenicity and explain the different manifestations of the disease.

**Introduction**

The genus *Streptococcus* is a gram-positive coccus which grows in chains. *Streptococci* are classified into an α-, β- and γ-haemolysis group based on the type of haemolysis exhibited. Lancefield classified the beta-haemolytic group into subgroups according to a polysaccharide in its membrane. They were labelled with capital letters from A to W. Beta-haemolytic Group A streptococcus (GAS), also known as *Streptococcus pyogenes* (S. pyogenes) is known as an infective agent of respiratory infections and certain skin infections. The throat and skin of the human host are the principal reservoirs for *S. pyogenes*. Pharyngitis and impetigo are the most frequent diseases caused by it. Other less common manifestations of this infectious agent include otitis media, mastitis, necrotizing fasciitis, osteomyelitis, meningitis, septic arthritis, endocarditis, pericarditis and scarlet fever.

Despite being recognized for many years, the aetiology of GAS associated sepsis and the streptococcal Toxic Shock Like Syndrome (TSLS) remains poorly understood. It has been demonstrated that an unexplained resurgence in the prevalence of invasive GAS infection has occurred over the past 30 years. The greater part of the more common infections is minor and self-limiting, but severe invasive infections and septic shock can occur. Until recently, not much was known about the factors that determine the differences in disease manifestation. Nowadays, attention focuses on host and pathogen properties and interactions, in an attempt to explain the variety in pathogenicity and the wide spectrum of clinical manifestations of this infection.

**Patient A**

A 45-year old woman was referred to the emergency department (ED) by her family physician with hypotension and tachycardia after a corticosteroid injection in the right hip. Her past medical history consisted of a HELPP-syndrome eight years previously, a uterus extirpation one year previously and hypertension for which she used metoprolol, hydrochlorothiazide and valsartan. She was allergic to soy-products and band aids.

She complained of a one week history of malaise and upper respiratory tract symptoms. One day before her presentation to the ED she developed nausea, light-headedness, diarrhoea, limb weakness and right sided hip pain. Her vital signs on admission were: blood pressure 80/40 mm Hg, heart rate 100 bpm and a temperature of 37.5 degrees Celsius. Her oxygen saturation was 99% without supplemental oxygen. Further physical examination was normal, except for erythema of the chest and abdomen, moderate cervical adenopathy and localized tenderness over the great trochanter of the right hip without any swelling or erythema.

Laboratory examination revealed: CRP 129 mg/L (normal value 0-6), leucocytes 12.1 /nl (4.0-10.0), creatinine 179 μmol/L (64-104), BUN 6.9 mmol/L (2.5-6.4), sodium 133 mmol/L (135-145), potassium 3.2 mmol/L (3.5-4.8), bilirubine 19.9 μmol/L (0.0-17.0), amylase 66 U/L (<100), ASAT 42 U/L (<35), ALAT 56 U/L (<45), g-GT 71 U/L (<55), alkaline phosphatase 88
U/L (43-115), LD 191 U/L (<248), troponine-t 69 ng/L (<30), CK 4600 U/L (<145), BNP 3666 pmol/L (<15). Ultrasound studies of both abdomen and right hip showed no abnormalities and X-rays of the chest and the right hip were normal as well.

The patient was treated with a combination of piperacillin and tazobactam after withdrawal of blood cultures. She developed a high fever and a progressive skin rash and increasing doses of norepinephrine (up to 0.95 mcg/kg/min) were necessary to maintain a mean arterial pressure of 65 mm Hg. Because of high values of troponine-t (maximal value 740 ng/L, normal <30) a cardiac ultrasound was performed, but no abnormalities were found. The patient developed acute renal failure, staged as ‘failure’ according to the Rifle criteria. Continuous hemofiltration was started with a blood flow of 200 ml/min and a substitution volume of 2.5 L/hr, 80% predilution and 20% postdilution. Ultrafiltration was set at zero ml/hr. Hereafter she was intubated and mechanically ventilated because of rapidly developing respiratory insufficiency and a lactic acidosis.

Because of progressive worsening of the PaO2/FiO2 ratio the patient was placed in the prone position. Two days after admission, all blood cultures were positive for GAS. Her antibiotic therapy was switched to penicillin in combination with IV clindamycin. We discussed the use of intravenous immunoglobulin and decided to give her intravenous normal human immunoglobulin at a dosage of 2 g/kg. Unfortunately the patient’s hemodynamic condition deteriorated and despite high doses of norepinephrine (1.95 mcg/kg/min) in addition to terlipressine 20 µg/kg 6 times a day, she died three days after admission to the ED. Her husband and daughter were treated with azitromycin for five days. Autopsy results and microscopic examination showed severe ARDS, acute tubular necrosis and necrosis of the heart muscle. Remarkable was the extensive skin disorder (figure 1) On multiple microscopic examinations of different skin parts, superficial extravasations of red blood cells were seen, especially in the papillary dermis. No myositis or fasciitis was seen.

**Patient B**

A 35-year old woman was referred to the ED with a two day history of headache, right sided ear pain, right sided otorrhoea and fever. Her past medical history was unremarkable. Just before admission she had developed neck stiffness and confusion. Her vital signs on presentation were: blood pressure 115/62 mm Hg, heart rate 90 bpm and a temperature of 38.7 Celsius. Her oxygen saturation was 98% without supplemental oxygen. Lumbar puncture showed milky fluid with an increased protein level of 1340 mg/L (normal value 150-500 mg/L), decreased glucose 0.6 mmol/L and a high leucocyte count of 4073 /µl (normal value <12). She was treated for bacterial meningitis with intravenous dexamethason, amoxicillin and ceftriaxon and she was transferred to the ICU. A few hours later the cerebrospinal fluid gram stain showed gram-positive cocci. Antibiotic therapy was switched to penicillin. Dexamethason was continued for four days. No hemodynamic or respiratory problems occurred. Because of persistent otorrhoea, an ENT specialist was consulted. He ruled out mastoiditis and diagnosed an acute otitis media. When blood cultures appeared to be positive for GAS, clindamycin was added to the penicillin. Her clinical condition improved quickly and one day after admission she could be transferred to the neurology ward.

**Patient C**

A 73-year old man was admitted to the ED with a three day history of dyspnoea and a one day history of a painful, red knee. His past medical history consisted of a locally advanced rectum carcinoma for which he had been treated with chemo-radiation and a rectum amputation, a coronary artery bypass grafting, mitral valve insufficiency, carotid endarterectomy, COPD, diabetes, hypertension and chronic lymphatic leukaemia for 2.5 years. He was on prednisone, tolbutamide, lisinopril, mono-cedocard, furosemide, labetalol, metformine, diclofenac, misoprostol, carbaspirin, calcium and tamsulosine.

The patient came to our ED after tripping and falling on his head. He hadn’t lost consciousness and there was no nausea...
or vomiting. There was no fever or malaise, no chest pain or cough. Physical examination revealed a blood pressure of 111/58 mm Hg with a heart rate of 97 bpm, a temperature of 39.9 Celsius and an oxygen saturation of 94% with 2 L/min of supplemental oxygen. He had a small hematoma on his left temple and an abrasion of his left eyebrow. Neurological examination was normal. Auscultation of the heart and lungs revealed normal heart sounds and mild crackles over both lungs. Examination of his abdomen was normal. There was pitting edema on both ankles. His right knee was red, warm, swollen and very tender to palpation. There was erythema and oedema of the right lower leg (figure 2). A puncture of his right knee did not show growth of bacteria. His chest X-ray showed cardiomegaly and prominent hili. Laboratory examination revealed leucocytes of 20.4/nl (4.0-10.0), CRP 302 mg/L (0-6), sodium 129 mmol/L (135-145), potassium 4.7 mmol/L (3.5-4.8), BUN 14.7 mmol/L (2.5-6.4) and a creatinine of 197 µmol/L (64-104). He had elevated cardiac enzymes with a troponine-t of 1904 ng/L (<30) and a CK of 2335 U/L (<171). His ECG showed no new abnormalities. He was diagnosed with erysipelas accompanied by a non-ST-elevated myocardial infarction and was admitted to the general ward for cardiac rhythm observation. Two days later he suddenly fainted while sitting in his chair. He had a fever (39.4 Celsius), blood pressure 60/40 mmHg with a heart rate of 80 beats per minute and an oxygen saturation of 74%. His saturation responded well to supplementary oxygen but because of persistent hypotension despite aggressive fluid therapy, he was transferred to the ICU for treatment with norepinephrine. A sonogram of his left leg did not show thrombosis. His blood cultures were positive for streptococci, which turned out to be GAS. He was treated with penicilline and clindamycin, to which he responded well. An echocardiogram did not show endocarditis. 72 hours later he was discharged to the surgical ward.

**Discussion**

In this paper we have described three patients suffering from GAS infection. One patient died, one patient had minor symptoms and one patient suffered from septic shock. Most GAS infections are relatively mild. On rare occasions, as in our first and third cases, GAS may cause severe and even life-threatening diseases. At first sight it is often unclear why GAS presents in so many different ways in different patients, but substantial evidence shows that factors in both host and pathogen may cause the broad heterogeneity in disease manifestation of this microorganism.

**Heterogeneity in disease manifestation**

**Factors within the pathogen**

Several virulence factors of GAS are involved in the pathogenesis of toxic shock, invasion of soft tissues and skin, and necrotizing fasciitis. The pathogenicity is derived from components of the cell wall, as well as extracellular products. These virulence factors are the M protein, extracellular pyrogenic exotoxins A, B, and C as well as other exotoxins and superantigens such as exotoxin F (mitogenic factor) and streptococcal superantigen.6-9 Currently, the M protein is thought to be the major virulence factor of GAS. This protein plays an important role in the properties of the microorganism to colonize, to evade phagocytosis and in the mechanisms that allow the invasion of sterile sites. To date, more than 200 M protein serotypes have been identified. Infection with specific serotypes (M protein types) is more likely to result in severe clinical reactions (e.g. rheumatic sequelae) and specific clinical outcomes such as puerperal sepsis and necrotizing fasciitis.4 The M protein is a major filamentous surface protein of GAS and is the determinant of type-specific immunity. It is a coiled-coil dimer and is essential for the virulence of GAS. The carboxy-terminus, anchored in the cell wall, contains conserved epitopes, whereas the more distal amino terminus displays the characteristic type-specificity. Parts of the M protein have shared antigens and cross reactivity between these epitopes and human proteins may be the source of autoimmune sequelae. After an infection, long lasting immunity exists for the specific serotype. The N-terminal region is most likely to be bound by antibodies, containing an extremely variable domain associated with the serotype identity.10 The M protein is necessary for adhesion to cells. Several M proteins can activate the coagulation system by binding kininogen and generating bradykinin, while M1 and M3 have been shown to trigger human monocytes and endothelial cells. M1 and M5 can bind to fibrinogen and can recruit and activate platelets, causing thrombosis in some cases. In conclusion, M proteins have the ability to activate platelets, which in turn can activate neutrophils and monocytes, amplifying the pro-inflammatory effect.11

**Figure 2.** Patient C: Erythema and swelling of the right lower leg.
Functionally, the M proteins inhibit phagocytosis. M proteins are distinguished by their ability to produce an apoproteinase that cleaves apoprotein A1, also termed Serum Opacity Factor.

Serotyping of GAS based on the M protein has long been used as the gold standard for the typing of this pathogen. Nowadays, it has been replaced by sequencing the hypervariable region of the emm gene coding for the M protein, but the two methods are extremely well correlated. A website (http://www.cdc.gov/ncidod/biotech/strep/strepblast.htm) has been established from which an emm sequence database can be downloaded for emm typing.

Some aspects of the type-specific outcomes derive directly from virulence properties of the M protein which is coded by the emm gene. Serology or emm typing can reveal the M type. The content and chromosomal arrangements of the 4 emm subfamily genes are arranged in 5 patterns, from A to E. The emm pattern A–C isolates are found to be associated with the nasopharynx, whereas emm pattern D strains are most often isolated from skin and impetigo lesions. Organisms of emm pattern E are found at both tissue sites.

A variation in the virulence of GAS may lie in the structure of the emm genes that encode the M proteins. Death or a severe outcome due to GAS infection is associated with types M1, M3 and M12. M28 is related to puerperal sepsis; M1, M3 and M18 to TSLS. Nearly all M1 and M3 strains produce Streptococcal Pyrogenic Exotoxin (Spe) A. M18 produces Spe C. Epidemic acute rheumatic fever is associated with M5 and M18. Geographical spread is most commonly associated with M1.

The M proteins as well as some other streptococcal proteins are responsible for post-infection autoimmune sequela. The association of these proteins with virulence is certainly present in some cases but the expression of virulence varies according to phenotypic and genotypic characteristics. Some aspects of the GAS pathogenicity and the specificity of the disease are changed by local mutations, rather than by the presence or absence of specific genes.

Some other determinants of virulence are encoded by other chromosomal genes for which the links to virulence is far less clear. It is remarkable to see that a substantial number of invasive streptococcal infections have no known portal of entry. Transient bacteraemia originating from the oropharynx has been suggested as the source of the infection in such cases.

At present, knowledge of the type of M protein does not have a scientifically proven benefit in the treatment of GAS. However, typing of the M protein is used for studies of the geographic spread of different types of GAS. On top of that it may be of value for the preparation of vaccines and sensibility studies for antibiotics. Because different M proteins have different virulence, we believe that in the future M protein typing may be useful in clinical treatment and might be of help in important clinical decision making such as immunoglobulin treatment, timing of surgery etc.

Superantigens (SAgs)

Superantigens are immune-modulatory proteins produced by pathogenic microbes, which stimulate T-cells and antigen presenting cells (APC) such as macrophages by direct and nonspecific binding of Major Histocompatibility Complex (MHC) II with T-cell receptors. This results in a massive cytokine production and subsequent systemic effects of sepsis and septic shock. In S. pyogenes infections, this is called the Toxic Shock Like Syndrome (TSLS). TSLS is known for its fulminant course, resembling Toxic Shock Syndrome (TSS), which is caused by certain types of Staphylococcus bacteria. Although the earliest cases of TSS involve women who were using tampons during their periods (menstruation), today less than half of current cases are associated with such events. Some M proteins of GAS, such as M5, may act as superantigens. These superantigens might play a role in scarlet fever and TSLS as well. GAS also produces other SAgs, such as SpeA, SpeB, SpeC, SpeF, SpeG, SpeH, SpeI, SpeJ, ssa, and smeZ.

Compared to a normal antigen-induced T-cell response, T-cell activation by SAgs is polyclonal. The unique ability to interact simultaneously with MHC II class molecules and T-cell receptors leads to the formation of a trimolecular complex. This complex induces profound T-cell proliferation, which results in giant cytokine release, causing epithelial damage with subsequent capillary leak and hypotension. Some SAgs are capable of activating one in four of the body’s T-cells or more, compared to 1 in 1000 or 1 in 10000 T-cells in a normal reaction.

The majority of SAgs of GAS are capable of binding to MHC class II receptors via high affinity zinc binding. Zinc-dependent binding facilitates the deposition of SAg molecules upon the antigen presenting cell surface, leading to further T-cell activation. SpeA and SpeC are capable of forming monomeric dimers, which are able to interact with two MHC II molecules (and/or T-cell receptor) simultaneously. SAg exposure can enhance the Toll Like Receptor response to Gram negative lipopolysaccharide, thus enhancing TNF cytokine responses. SAgs may therefore contribute to the pathophysiology of sepsis through up regulation of the proinflammatory cytokines TNF-α, IL-1β, and IL-6. The ability of SAgs to interact with epithelial cells has been demonstrated using a variety of cell lines.

Toxic Shock Like Syndrome (TSLS)

GAS is responsible for TSLS, and most recently it has gained notoriety as the “flesh-eating” bacterium which invades the skin and the soft tissues. Fever and a “sunburn like rash” are features of TSLS. Hypotension is present in about 50% of all
cases. Desquamation of the skin occurs about two weeks after presentation. Septic shock and ARDS can subsequently develop leading to multi-organ failure. TSLS nearly always occurs in association with bloodstream invasion by the causative streptococci and often occurs in the presence of necrotizing fasciitis and myositis. Almost all group A streptococci associated with TSLS produce one or both of the two SAgs A and/or C. Spe proteins A–D, F–H and J, and other proteins including SAgs and the streptococcal mitogenic exotoxins smeZ and Z-2 are a diverse group of virulence factors capable of inducing TSLS. In addition, several superantigens with strong mitogenic activity have been reported. M18 strains nearly always produce Spe C, explaining its association with TSLS. Some produce Spe A as well. Research is trying to reveal a plausible model for the comprehensive evolutionary pathway of streptococcal (and staphylococcal) SAgs. Scarlet fever and TSLS

Scarlet fever or scarlatina is caused by group A streptococci that produce exotoxins (e.g. scarlet fever toxin). It’s a childhood disease and commonly affects 4–8 year-old children. Symptoms include a sore throat, fever, a strawberry tongue and a characteristic red rash. The clinical features are caused by the erythrogenic toxin, a substance produced by GAS. Although TSLS is different compared to scarlet fever, the two diseases do have similarities. Both can occur in young and healthy people, both are associated with a high mortality and both produce essentially the same exotoxin, streptococcal pyrogenic exotoxin.

Factors within the host

The outcome of infection depends not only on bacterial factors but also on host factors. In the study by Koth et al., higher rates of GAS were found in older patients and in males compared to females. Environmental factors (such as poverty and crowding, e.g. crowding in schools) may also play a role in the development of invasive GAS. The most common risk factors are skin conditions like varicella, psoriasis, traumatic skin lesions and the use of intravenous catheters. Necrotizing fasciitis due to GAS was 5.97 times more likely in patients with a recent history of blunt trauma. Influenza, diabetes, malignancy, drug abuse and heart disease are also risk factors. Lastly, the postpartum period confers a substantial elevation in risk. The response of the host to SAgs plays a role in the severity of the clinical symptoms. Cytokine response patterns and the presence of anti-streptococcal antibodies or antitoxin antibodies play a major role in this. The severity and potential invasiveness of colonization by a strain is limited in patients who have been infected with that same strain before, which can be explained by the presence of type-specific antibodies in those patients. Specific host HLA alleles are involved in the development of TSLS and acute rheumatic fever. It has been shown that severe invasive diseases caused by GAS, including TSLS, are linked to the responsiveness of the host to an interaction of the SAg with the MHC II molecule on APC’s. A severe APC response, with massive cytokine production, leads to TSLS with or without necrotizing fasciitis, whereas an attenuated APC response to SAg leads to pharyngitis. Bacteraemia without a focus is found in 15% of the cases of invasive GAS disease. In a study on invasive GAS diseases in children with primary varicella infection in the United States, an association was found between ibuprofen use and invasive GAS infection.

Necrotizing fasciitis

GAS necrotizing fasciitis is a critical emergency, which requires an early diagnosis, prompt and repeated surgical intervention and broad-spectrum antibiotic therapy. The operative findings in necrotizing fasciitis include the presence of a greyish necrotic fascia, a lack of bleeding of the fascia during preparation and the presence of foul smelling pus. Tissue specimens for culture and histology are crucial and should be performed for all patients without exception. Surgical debridement is the mainstay of treatment of necrotizing fasciitis and results in significantly improved mortality compared to cases in which surgery is delayed for even a few hours. Controversy exists on how much tissue should be excised. In many cases the surrounding skin appears normal, when it is actually necrotic or has extensive vascular thrombosis as well as vasculitis. Aggressive surgery is associated with significant morbidity though, and patients are left with complex wounds and extensive tissue loss. Caution should be exercised whenever patients present with a benign clinical presentation and no intraoperative evidence of infection can be found, even though benign clinical pictures resembling necrotizing fasciitis are relatively rare. The role of hyperbaric oxygen therapy is not entirely clear either. If available, it can be considered in the hemodynamically stable patient, but should never interfere with or delay the (repeated) surgical treatment. It continues to be the subject of scientific analyses and new studies.

Diagnosis of GAS

The diagnosis of the TSLS is based on criteria published in 1993 (table 1). Complications of GAS infections are acute post-streptococcal glomerulonephritis and acute rheumatic fever which are both immunologically mediated.

Treatment of GAS

Antibiotic therapy

Penicillin, to which group A beta-haemolytic streptococci are uniformly susceptible, is the first-line antibacterial therapy of choice for invasive infections. Clindamycin is a very

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**Heterogeneity in ‘Streptococcus pyogenes’ infections in the ICU, a case series**

**Diagnosis of GAS**

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**Treatment of GAS**

Antibiotic therapy

Penicillin, to which group A beta-haemolytic streptococci are uniformly susceptible, is the first-line antibacterial therapy of choice for invasive infections. Clindamycin is a very
important adjunctive antibiotic because of its anti-toxin effects and excellent tissue penetration. Clindamycin has proven its additional value in cases of septic shock. In experimental models of invasive GAS infection, clindamycin even has greater efficacy than penicillin, since it potentiates phagocytosis and has a longer lasting antibacterial effect.

**Intravenous immunoglobulin**

The administration of intravenous immunoglobulin (IVIG), which is generally advocated in such cases in the USA, is thought to neutralize the exotoxins. All three streptococcal exotoxins A, B and C are inhibited by IVIG. To date, the effectiveness of this therapy has not been established, but limited clinical experience suggests marked improvement in some TSLS patients after having received intravenous high dose immunoglobulin. This is why, even in the absence of conclusive data, the potential benefits make its use reasonable in life-threatening cases. IVIG therapy has been advocated in order to lower the mortality in TSLS. IVIG has been shown to inhibit T-cell proliferation and production of cytokines. Furthermore, other anti-inflammatory properties are attributed to IVIG, just as the neutralizing antibodies against streptococcal superantigen toxine.

**Treatment of family members**

People living in close contact with each other are at risk of getting an invasive GAS infection. This means that family members as well as friends and colleagues of patients suffering from GAS are at risk of becoming sick as well. Dutch infection prevention guidelines advise treating family members and other persons living in close proximity of the diseased person with azitromycine. The spread of GAS has been described in hospitals and will have to be thoroughly examined, especially when more than one patient is diagnosed in the same hospital. Several epidemiological studies have shown that GAS incidence is increasing.

**Case reflection**

**Case A**

Patient A had positive blood cultures for GAS without an identified local illness other than a sore throat. She developed severe multi organ failure including diffuse intravascular coagulation (DIC). We believe that this patient belongs to the group of 15% of GAS patients without local symptoms. The dramatic clinical course did give rise to a suspicion of fasciitis, endocarditis or even toxic scarlet fever, but no clinical data demonstrated this. Unfortunately, on post-mortem examination no further explanation could be given for the GAS septic shock.

**Case B**

Patient B appeared to have meningitis caused by GAS. Bacterial meningitis is a rare manifestation of GAS infection. Although over the past decade an increased incidence and severity of invasive GAS infections have been reported by several authors, GAS remains a very uncommon cause of bacterial meningitis, especially in adults. In children, it accounts for about one percent of all childhood meningitis. But even though GAS meningitis is uncommon and the incidence seems to be persistently low, clinicians should know that sporadic cases do occur. And although in our case the infection responded very well to antibiotic treatment, there have been several cases reporting a fulminant course with a relevant neurological sequel. Despite a high mortality, the illness is easily treatable if diagnosed early since the bacterium retains its sensitivity to many antimicrobials. Penicillin is the drug of choice in GAS meningitis.

Reports have suggested that a focus for the initial infection can be identified in 68% of all GAS meningitis cases, with otitis media being the most common. Children with cochlear implants are at increased risk and a change in the child’s hearing is often noted first.

**Case C**

Patient C had positive blood cultures and a lesion on his leg that resembled erysipelas. GAS is considered the primary cause of erysipelas and invasive infections are a common reason for hospitalization. Serious forms may occur in patients with no known risk factor, including young patients. Quite often this condition is observed in the elderly population with a more vulnerable venous system.

**M proteins**

The *emm* genes coding for the different M proteins were determined in all three patients. GAS isolated in patient A was typed as *emm* type 3.1. The same type was found in patient C. GAS in patient B was typed as 5.1. Infection with *emm* type...
3 is associated with an increased risk of TSL5. Reference 1 Emm 1 and emm 3 strains were the most frequent strains found in invasive GAS disease. This explains the severe hypotension observed in patient A and C. For emm type 5 no specific properties or virulence patterns were given. Meningitis caused by GAS occurs seldom.

Conclusion

Streptococcus pyogenes can cause a broad variety of clinical pictures and recognition of severe syndromes like TSLS and necrotizing fasciitis is of utmost importance. New insights have been gained regarding virulence factors within both host and pathogen. When it comes to the host, it seems that besides the well-known risk factors like age, sex and skin lesions, the response of the APC plays a major role in disease manifestation. When it comes to the pathogen, currently the M protein is thought to be the major virulence factor of GAS. While TSLS is caused by different M serotypes, it is particularly associated with M1 and M3 strains. In addition a high rate of certain SaGs, especially the encoded Spe A has frequently been reported among TSLS-associated isolates compared to those who recovered from superficial infections. More research needs to be done to elucidate the (possible) relevance of this association.

References


A 44-year-old woman reported to the emergency department because she experienced an acute deteriorated vision in her left eye. Apart from hyperthyroidism, treated medically, she was healthy. There was no history of headache, pain, trauma, fever or previous ophthalmological conditions. The patient did not wear glasses or lenses and worked as a first responder ambulance nurse.

On examination, the patient’s vital signs were normal. There was a striking anisocoria, with an evidently dilated right pupil which was only slightly reactive to light, and a normal pupil reaction in the left eye. There was no tearing of the eye, and no bulging or reddening of the sclerae/conjunctival erythema. Vision in the right eye was 1.0 and the left eye had a vision of 0.9. In retinoscopy, both maculae and retinae were unremarkable. Eye movements were normal. No ptosis of the eyelids was seen. On palpation of the neck, no abnormal swellings or lymph nodes were found.

On further history taking, she reported to have handled a broken ampoule of atropine that day. In retrospection, this image equals the clinical presentation of patients in whom atropine droplets have been applied for ophthalmic examination. The loss of vision in the left eye was explained by persistent contraction of the left pupil due to constant light exposure in the right eye.

This case illustrates that circumstances in a patient’s occupation can be the key to finding the diagnosis. A person’s work environment or substance handling are of unequivocal importance in history taking.
## Conferences

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<tr>
<td>24-25 April</td>
<td>11th Annual Critical Care Symposium 2014</td>
<td>Manchester, Mercure Manchester Piccadilly Hotel</td>
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<tr>
<td>8-10 May</td>
<td>61st Annual Meeting 2014 German Society Of Anaesthesiology And Intensive Care</td>
<td>Congress Center Leipzig, Germany</td>
<td><a href="http://www.dac2014.de/">http://www.dac2014.de/</a></td>
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<td>LIVES 2014, the 27th ESICM Annual Congress</td>
<td>Barcelona, Spain (CCIB)</td>
<td><a href="http://www.esicm.org/events/next-congress#sthash.mKg9FHCv.dpuf">http://www.esicm.org/events/next-congress#sthash.mKg9FHCv.dpuf</a></td>
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<td>44th Critical Care Congress</td>
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<td><a href="http://www.sccm.org/Education-Center/Annual-Congress/Pages/default.aspx">http://www.sccm.org/Education-Center/Annual-Congress/Pages/default.aspx</a></td>
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<td>3-7 October</td>
<td>LIVES 2015, the 28th ESICM Annual Congress</td>
<td>Berlin, Germany (CityCube Berlin)</td>
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**Methods and results**

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• The names of hospitals should be written in English.
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• ± is a mathematical symbol and should not be used in a non-mathematical context to mean approximately or about.
• Generally, organizations and groups of people take single verbs, e.g. the team has researched.

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<th>Acronym</th>
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<td>AIDS</td>
<td>acquired immunodeficiency syndrome</td>
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<td>ALI</td>
<td>acute lung injury</td>
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<td>ARDS</td>
<td>adult respiratory distress syndrome</td>
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<td>APACHE</td>
<td>acute physiology and chronic health evaluation</td>
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<td>BIPAP</td>
<td>biphasic positive airways pressure</td>
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<td>CCU</td>
<td>coronary care unit</td>
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<td>COPD</td>
<td>chronic obstructive pulmonary disease</td>
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<td>CPAP</td>
<td>continuous positive airway pressure</td>
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<td>CT</td>
<td>computerized or computed tomography</td>
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<td>electrocardiogram</td>
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<td>extracorporeal membrane oxygenation</td>
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<td>electroencephalogram</td>
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<td>ELISA</td>
<td>enzyme-linked immunosorbent assay</td>
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<td>ETCO2</td>
<td>end-tidal carbon dioxide</td>
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<td>HDU</td>
<td>high dependency unit</td>
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<td>HIV</td>
<td>human immunodeficiency virus</td>
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<td>IC</td>
<td>intensive care</td>
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<td>ICU</td>
<td>intensive care unit</td>
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<td>IM</td>
<td>intramuscular</td>
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<td>INR</td>
<td>international normalized ratio</td>
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<tr>
<td>IPPV</td>
<td>intermittent positive pressure ventilation</td>
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<tr>
<td>IV</td>
<td>intravenous</td>
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<tr>
<td>MAP</td>
<td>mean arterial pressure</td>
</tr>
<tr>
<td>MODS</td>
<td>multiorgan dysfunction syndrome</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>PACU</td>
<td>post anaesthesia care unit</td>
</tr>
<tr>
<td>PEEP</td>
<td>positive end expiratory pressure</td>
</tr>
<tr>
<td>PET</td>
<td>positron emission tomography</td>
</tr>
<tr>
<td>SARS</td>
<td>severe adult respiratory syndrome</td>
</tr>
<tr>
<td>SIRS</td>
<td>systemic inflammatory response syndrome</td>
</tr>
<tr>
<td>SOFA</td>
<td>sequential or gan failure assessment</td>
</tr>
<tr>
<td>SPECT</td>
<td>single-photon emission ct</td>
</tr>
<tr>
<td>TIA</td>
<td>transient ischemic attack</td>
</tr>
<tr>
<td>TRALI</td>
<td>transfixion-related acute lung injury</td>
</tr>
</tbody>
</table>

Table 2