ISSN: 2475-6296

Research Article

Journal of Clinical & Experimental Immunology

Role of Hypothalamic Pituitary Adrenal (HPA) Axis and Tumor Necrosis Factor (TNF) in Development of Post-Traumatic Nosocomial Pneumonia

T. Mózes[1*], K. Gornicsar[2], A. Grosz[1], Ta. Mózes[3], Kh. Diab[1] and E. Madarász[4]

[1]*Military Hospital, Budapest, Hungary.*

[2]*Dept. of Urology, Péterfy Hospital, Budapest, Hungary.*

[3]*Dept. of Psychology, EötvösLoránd University, Budapest, Hungary.*

[4]*Inst. of Exp. Medicine of Hung. Acad. Sci*

[*]Corresponding author
Tibor Mózes, Military Hospital, Budapest, Hungary, Tel: +36 30 231 4252; E-Mail: mozes.tibor@gmail.com.

Submitted: 10 Sep 2017; **Accepted:** 18 Sep 2017; **Published:** 24 Sep 2017

Abstract

Background and purpose: *Infection after experimental focal ischemia may result from brain-induced immune depression. A strong cytokine mediated anti-inflammatory response was recently observed in stroke patients at higher risk of infection, although infection due to the decreased pro-inflammatory mediators can be expected as well. To investigate this question the following experiment was performed.*

Methods: *105 over 60 years hip fracture patients were included in the study. Sera and lympho/monocytes were separated from blood samples taken on different days (day 1, 3, 6, 9). Isolated lympho/ monocytes were cultured for one day with or without endotoxin (LPS). TNFα levels in sera and in the culture supernatants were determined by bioassays using WEHI 164 cells. Plasma ACTH and cortisol values were measured by RIA kits.*

Results: *From 105 hip fracture patients 7 nosocomial pneumonia patients were found, (4 survivors and 3 non-survivors) furthermore 2 non-survivors with cardiovascular death without infection. On the day of trauma the level of circulating TNFα activity was extremely low in nosocomial pneumonia patients in comparison to uneventful healing patients. In pneumonia patients TNFα started to increase on day 3, increased till day 9 then reached the values of uneventful healing group. In two patients with later cardiovascular complications, extremely high TNF alpha activities were detected throughout the entire observation period. The plasma cortisol values were high in nosocomial pneumonia patients in comparison to uneventful healing persons, and decreased slightly by the 9th post-trauma day. In the two cardiovascular patients, serum cortisol was extremely low on the day of trauma and increased gradually during the investigation period. ACTH level was stable in the sera of uneventfully healing patients, while showed large individual and also time-dependent fluctuations people with post-traumatic complications.*

Conclusions: *An excessive decrease in pro-inflammatory response is a key facilitating factor for the development of infection.*

Introduction

Hip fractures in the geriatric population are a major public health problem. Worldwide, elderly people represent the fastest growing age group; the yearly number of fractures is likely to rise substantially with the continued ageing of the population. Even if incidence rates for hip fracture remain stable, the estimated number of hip fractures worldwide will rise to 6.26 million by 2050 [1].

Given the fact that isolated hip fractures (IHFs) in the elderly significantly influence risk-adjusted outcomes and are variably reported by trauma centers (TCs) these patients should be excluded from subsequent benchmarking efforts [2].

The Dutch Trauma Trial, a prospective, randomized, double-blind, placebo-controlled study of antibiotic prophylaxis in the primary operated limb fractures of 2195 patients were included. The rate of nosocomial infection in the first month was 10.2% with placebo. Most of the fractures were located in the hip 867 with 23 pneumonia indicating the majority of hip fracture among limb fractures and leading nosocomial infection [3].

Hospital-acquired pneumonia (HAP), defined as pneumonia occurring 48 hours or more after admission, is the second most common nosocomial infection among patients in the intensive care unit (ICU). Among hospital-acquired infections, HAP is associated with the highest number of deaths The primary risk factor for the development of HAP is mechanical ventilation what is not common in hip fracture [4, 5].

Severe illness and stress strongly activate the hypothalamic-pituitary-adrenal (HPA) axis and stimulate the release of adrenocorticotrophic hormone (ACTH) from the pituitary, which in turn increases the release of cortisol from the adrenal cortex [6-8]. This activation is an essential component of the general adaptation to illness and stress and contributes to the maintenance of cellular and organ homeostasis. Adrenalectomized animals succumb rapidly to hemorrhagic and septic shock, and steroid replacement is protective against these challenges [9, 10].

Stressful early life experiences can have short- and long-term effects on neuroendocrine and immune mechanisms of adaptation, which are primarily modulated by glucocorticoids. One study aimed to examine how the stress and immune systems interact to cope with psychosocial stress induced by a single social isolation.This social isolation provoked increased plasma ACTH and cortisol concentrations and reduced TNF-levels but had no significant effect on IL-6 levels. Single social isolation also induced a dose-dependent cortisol resistance in LPS-stimulated PBMCs compared with controls, which may be an adaptive response in the short term. Moreover, LPS-stimulated cultures from control piglets showed a reduction in cortisol sensitivity with increasing age [11].

Respiratory failure is the most serious short-term complication of Guillain-Barre´ syndrome (GBS), occurring in 20% to 30% of patients. Reports indicated that plasma cortisol levels are higher in patients with GBS than in healthy subjects and are correlated with the severity of GBS [12]. However, its predictive value for occurrence of respiratory failure has not been assessed.

The spontaneous release of cytokines by macrophages from the noninvolved lung of pneumonia patients was comparable to that of macrophages obtained from lungs of healthy controls. After stimulation with LPS ex vivo, cytokine concentrations reached in cell culture supernatants were similar when cells from the involved lung and noninvolved lung of pneumonia patients were compared, but much lower than those measured in control subjects not suffering from pneumonia. This hypo responsiveness to in vitro LPS stimulation was not observed in the cultures of peripheral monocytes. These data are in line with reports on LPS hypo responsiveness of mononuclear cells from peripheral blood of patients with severe systemic infections, and in support the existence of a compartmentalized inflammatory response during pneumonia [13].

Patients with severe traumatic brain injury (TBI)) are at risk of the development of acute respiratory distress syndrome (ARDS). TBI and ARDS pathophysiologic mechanisms are known to independently involve significant inflammatory responses. The literature on the association between plasma inflammatory cytokines and ARDS in patients with TBI is sparse [14].

The brain and the immune system are functionally linked through neural and humoral pathways, and decreased immune competence with higher incidence of infections has been demonstrated in several acute neurological conditions. A strong cytokine mediated anti-inflammatory response was recently observed in stroke patients at higher risk of infection [15], although infection due to the decreased pro-inflammatory mediators can be expected as well. To investigate the question of the role of proinflammatory mediators in nosocomial infections the following experiment was performed.

Materials and methods

The study was approved by the ethics committee of hospital. One hundred five hip fracture patients were included in this experiment from January 1, 2009 till December 31, 2010. Subjects were admitted on the day of trauma and were operated on the day of trauma as well. Exclusion criteria were malignant disease, inflammation, infection, and taking non-steroid anti-inflammatory drugs and/or antibiotics. Manifestations of pneumonia were new or increased cough or purulent sputum production, clinical or new radiographic signs in the chest, and pyrexia above 38 °C. Tramado (ACTAVIS, Hungary an opiate receptor agonist) was used as a regular painkiller. Unfortunately the low number of observation does not allow calculating statistics. After obtaining informed consent, blood samples were taken from donors who had no physical exercise on the morning of blood sampling and had normal temperature.

The subjects studied are described in Table I.

Specimen Collection

A Vacutainer system was used for taking blood. Venous blood was collected in EDTA tubes. For best results, blood was processed for PBMCs within 2 hours. A separate tube was used for obtaining serum samples, which were stored at -20 °C until TNF alpha, ACTH and cortisol assays.

Isolation and treatment of peripheral blood mononuclear cells (PBMCs)

Seven ml whole blood was carefully layered onto the 7.0 ml of HISTOPAQUE®-1077 (Sigma, Hungary) in 50-ml conical tubes and was centrifuged at 400 g for 10 minutes at room temperature. After centrifugation, the opaque interface was carefully transferred into a clean conical centrifuge tube and mixed with 10 ml isotonic phosphate buffered saline (PBS; pH=7.2). After centrifugation (250g for 10 minutes), the cell pellet was resuspended in 12 ml PBS. The procedure was repeated 3-times in order to remove HISTOPAQUE contamination, then the cells were resuspended in RPMI 1640 with Hepes (Gibco, Paisley. UK) and L-glutamine, 0.8x10-3 mol/l supplemented with 5% bovine serum (referred to as culture medium (CM)). The cells were counted, distributed into minimum two aliquots and cultured as 106 cells/ ml CM with or without l□g/ml LPS, in round-bottomed polypropylene vials (38x 12.5 mm, Nunc, Roskilde, Denmark) in 5% CO2/humidified air at 37°C. LPS dose was selected by previous dose-effect calibration of LPS action on this system (0.1ng/ml-10000 ng/ml). After 24 h, the incubation was terminated by centrifugation at 250 g and aliquots of supernatants were stored at -80°C until TNF alpha measurements. Shorter incubation time (3 hours) demonstrated much lower TNF production by PBMCs.

Bioassays of TNF alpha activity

Ten µl aliquots of serum samples were diluted with 40 µl of serum-free Minimum Essential Medium (MEM; Sigma) in 96-well tissue culture plates, and 50 µl of suspension of WEHI-164 cells in serum-free MEM was added resulting in 2x104cells/well in 10% (patient's) serum containing fluid environment. For measuring TNF activity in lympho-monocyte conditioned media, 20 µl aliquots of culture media taken from lympho-monocyte cultures (grown in 10% FCS supplemented MEM) were added to micro-cultures of WEHI-164 cells (2x104cells/well) growing in 80 µl MEM medium supplemented with 10% fetal calf serum. Control cultures were grown in MEM supplemented with 10 % FCS. For calibration, WEHI-164 cells (2x104cells/well) were incubated with various concentrations (0.005

- 10 ng/ml) of human TNF alpha under the same conditions. WEHI cells were incubated for 24 hours at 37 °C with 5% CO2. At the end of the incubation, the viability of the cultures was determined by MTT-reduction method. Briefly, 50 µl of the culture medium was aspirated and 10 µl of 1.25 mg/ml stock solution of MTT in phosphate buffered saline was added (final MTT concentration of 0.125 mg/ml). After 1.5 hour incubation, 150 µl acidified (0.08 M HCl) isopropanol was added and the produced formazan was dissolved by trituration. The optical adsorption was determined at 570 nm (measuring) and 630 nm (reference) wavelengths in a micro plate reader (MWG-BIOTECH/BioRad).

Each data point was determined as the mean ± SD of data obtained from 4 sister cultures. The viability was calculated as the percentage of the optical density of controls (100%). The viability values were converted to TNF alpha concentrations by the equation obtained by viability determinations at defined TNF alpha concentrations.

TNF measurement of samples obtained from different subgroups of volunteers and sample taking were repeated in 3 months, 1 year and 9 years.

Hormone analyses

The analyses of ACTH concentrations were performed in duplicate on 200 µL of sera using a commercial 125I-IRMA kit (Immunotech, Marseille, France) according to the instructions of the manufacturer. The lowest level of ACTH that could be detected by this assay was 1.2 pg/mL, and intra- and interassay coefficients of variation were 9.1 and 9.6%, respectively. Serum cortisol concentrations were analyzed in duplicates using a commercially available 125I-RIA kit (Immunotech, Marseille, France) according to the manufacturer's instructions. The test sensitivity was 10 nmol/L, and intra- and interassay coefficients of variation were 5.8 and 9.8%, respectively. Clinical laboratory values like lymphocyte, counts, and γGT were assessed by routine clinical procedures.

Statistical analysis

All data are presented as means± standard error (SE mean).The data were evaluated by a non-parametric two way analysis of variance (Friedman test) followed by the Wilcoxon-Wilcox test to identify differences between measurements performed at different times during observation period. The Mann-Whitney test was performed to evaluate the differences between the groups. A P value of 0.05 or less was considered statistically significant for all tests. Correlation between serum cortisol and serum TNFα levels was calculated by Spearman rank test.

Results

From 105 patients 7 acquired pneumonia after 7,4 +/- 4,5 days of trauma and 3 died, Another 2 patients died for cardiovascular reasons free of infections. Unfortunately the low number of observation does' not allow to calculate statistical significance.

Descriptive statistics

		N
Type of fracture	Transcervical	41
	Pertrochanteric	49
	Subtrochanteric	15
Osteosynthesis	Dynamic hip screw	39
	Hemiathroplasty	1
	Gamma locking nail	25
	Screw fixation	40
Gender	male	30
	female	75
		Stat.
Age (y)	Mean	78,07
	Standard dev.	10,7

Table 1: demonstrates study population Surgery was performed on the day of admission what was the day of trauma

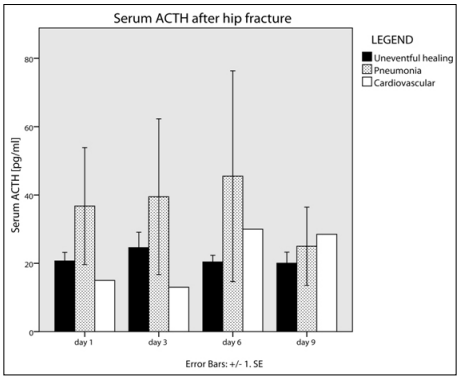

Figure 1: shows the changes in serum ACTH levels in different groups of hip fracture patients during observation period. ACTH levels were elevated in pneumonia group during the first 6 days after hip fracture.The small number (n=7) of cases does not allow drawing firm conclusions. Similarly SE calculation was not used neither in this nor in another figures in cardiovascular group of patients... Interestingly, both patients with cardiovascular complications (n=2) displayed low ACTH level during on the day 1 and 3 days after the trauma, a finding which may inspire further studies.

Plasma hormones and cytokine

Serum ACTH (Fig. 1), cortisol (Fig. 2), and TNFα (Fig. 3) concentrations indicated tendentious alterations between patients with different outcomes. On day1, serum ACTH was higher in the nosocomial pneumonia group (n=7) and was lower in the cardiovascular "group" (n=2) than in the uneventfully healing group. During the observation period (day 1-9), serum ACTH concentrations remained stable in uneventfully healing patients, while showed large individual fluctuations in the nosocomial pneumonia group with a tendency (statistically non-significant) of elevation.

Significantly higher cortisol concentrations were observed in nosocomial pneumonia group on day 1, and in comparison to uneventfully healing patients, elevated serum cortisol levels were sustained in the whole investigated period **(Fig. 2)**. Interestingly, the two patients with cardiovascular complications displayed decreased cortisol concentrations in the first three days. The TNFα activity in serum of nosocomial pneumonia patients was significantly lower than in uneventful patients, on day 1 and serum TNF started to increase later on **(Fig. 3)**. In the uneventful healing group, a stable elevation of serum TNF alpha activity was detected from day 3. Significantly enhanced serum TNF activity was found in the two cardiovascular patients throughout the entire observation period.

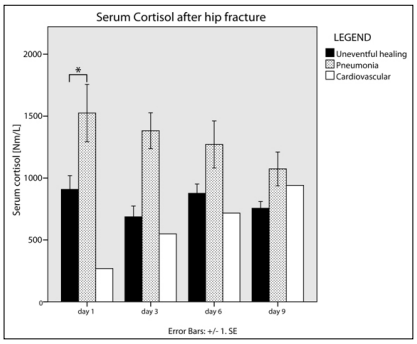

Figure 2: demonstrates the changes in serum cortisol levels in hip fracture patients during observation period. The serum cortisol levels during the first 3 days were significantly different from each other in three subgroups of patients. Mann-Whitney U test p< 0,05. The elevation observed in serum cortisol levels from day 1 till day 9 in cardiovascular "group" of patients was not significant statistically due to limited number of observations.

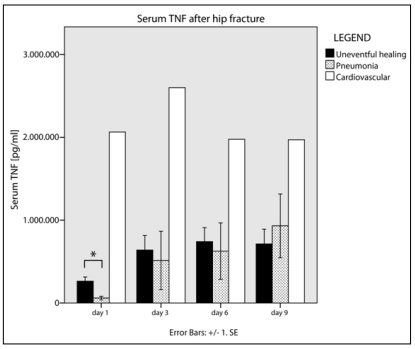

Figure 3: Changes in serum TNF alpha activity can be seen after trauma. On day 1 the circulating TNF alpha activity significantly differ in subgroups. Mann-Whitney U test p< 0.05. On day 3 only in cardiovascular patients was circulating TNF alpha activity elevated comparing to other subgroups of hip fracture patients. Statistical probes were not used as mentioned in Figure 1. To calculate statistically significant cshanges in TNF alpha levels and production is difficult due to marked inter-individual differences.

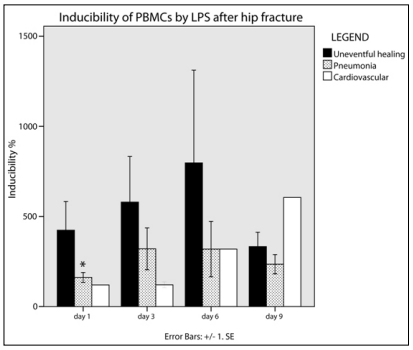

Figure 4: Changes in inducibility of PBMCs by LPS can be seen. A remarkable reduction in inducibility of pneumonia and cardiovascular groups was detected on day 1. Mann-Whitney U test p< 0.05. On day 3 changes were not significant due to limited observations. Similar problems were observed during later part of observation period. Despite this fact a clear tendency can be seen in cardiovascular "group" e.g. from day 1 till day 9 a gradual increase in inducibility occurs.

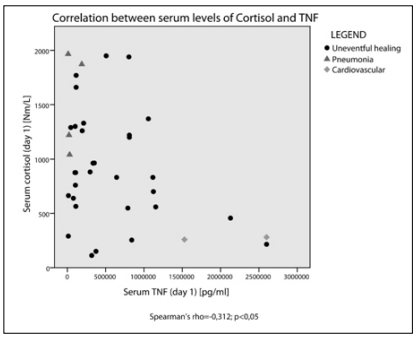

Figure 5: A significant negative correlation is demonstrated between serum cortisol and serum TNF alpha activity on day 1. Spearman rank test.

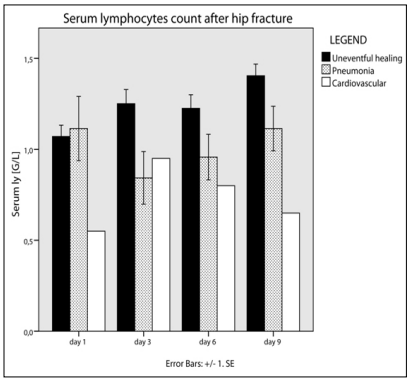

Figure 6: A severe lymphopenia was observed on day 1 after trauma irrespective of outcome. A fast recovery was observed in uneventfully healing group. This recovery delayed in pneumonia group. No recovery occured in cardiovascular "group" all 2 patients died.

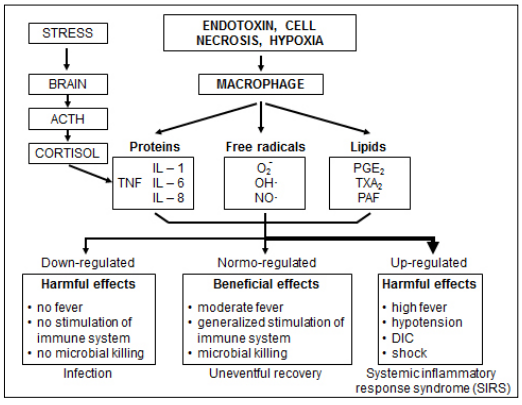

Figure 7. In the host response macrophage has a crucial role. It is stimulated, by microorganims, cell necrosis products and hypoxia. After stimulation macrophages produce different mediators including proteins, free radicals and lipids .The brain has lnfluence on the productions of mediators, mainly on protein synthesis through brain cortex, hypothalamic pituitary adrenal (HPA) axis and Tumor Necrosis Factor (TNF alpha) production. Finally, based on production of quantity, quality and ratio of each other of mediators, three different subgroups of host response can be seen: normo-regulated (majority of population) with uneventful healing and down-and unregulated forms. Both are harmful, in down regulated case no proper antimicrobial protection exists (pneumonia) while in prolonged up regulation no infection occurs but due to negative inotropic long term effect of TNF alpha a circulatory break down isobserved.

Discussion

The main findings of present study can be summarized as: (a) patients with uneventful healing and patients with nosocomial pneumonia show marked differences in respect of circulating TNF alpha activity. ACTH and cortisol levels as well as in the inducibility of PBMCs by LPS; (b) the TNF alpha activity ACTH and cortisol values outline down-, intermediate and up-regulated subgroups in the investigated population, on day 1 following hip fracture in respect of outcome as well (c) seven individuals in the "down-regulated" subgroup of hip fracture patients demonstrated high serum ACTH, cortisol levels and low serum TNF alpha activity and low inducibility of PBMCs by LPS all suffer of nosocomial pneumonia three of them died; (d) two patients demonstrated low serum ACTH, cortisol levels and higher serum TNF alpha activity with low inducibility of PBMCs by LPS, all patients died due to cardiovascular problems, free of infections: e) a negative correlation between serum cortisol and serum TNF alpha activity was demonstrated on day1 following hip fracture f) based on connection between brain and immune system three subgroups of host response to trauma were observed, the intermediate is beneficial, the down and up regulated are harmful resulting in either infection or cardiovascular problems: g) this different host responses can be seen on day 1 following trauma thus can predict the outcome.

Glucocorticoids (GC), the final mediators of hypothalamic pituitary-adrenal (HPA) activation, are important regulators of various physiological systems, including the immune system, and play a major role in the adaptation of organisms to stressful situations. Previous studies in humans and animals have shown that circulating GCs are beneficial during the adaptive process in the short run, but during long-term or repeated exposure to stressors, the effects of GCs on immune function are detrimental [6, 7]. Furthermore, it is well known that there are crucial interactive loops between GCs and cytokines. Proinflammatory cytokines, produced by activated immune cells, are potent activators of the HPA axis. GCs in turn suppress cytokine production and, by this mechanism, are able to terminate immune processes to protect the organism from an overactive immune system [8-10]. However our results suggest another explanation. On day 1 following trauma, ACTH and cortisol are elevated and TNF level is reduced indicate that host response to trauma and psychosocial stress is modified by HPA. HPA activated first and reduces the immune activity resulting in infection. Moreover if HPA activity is low TNF productivity will be higher, consequently no infection occurs but the host will die due to circulatory break down. A study suggests that GCs may cause alterations in cytokine production, which favor humoral immune responses while suppressing cellular immunity [15]. As present study demonstrated, the inducibility of PBMCs by LPS was reduced on day1 after trauma resulting in nosocomial pneumonia after 2 days. Although this model of immune deviation could be an adaptive mechanism to prevent the immune response from causing tissue damage, maladaptive responses to stress-induced immune alterations may contribute to increased disease susceptibility.

In addition to peripheral cortisol levels, the cortisol sensitivity of different target cells from organisms exposed to stressors should also be considered [16]. Several studies have supported the hypothesis that social stressors affect the steroid sensitivity of immune cells in animals and humans. As shown in mice, repeated social disruption stress may cause reduced cortisol sensitivity in splenocytes [17-21]. In addition, the corticosteroid sensitivity of peripheral blood lymphocytes was decreased in chronically stressed caregivers of patients with dementia [22]. Our results, gradually increasing levels of circulating TNF and inducibility of PBMCs during observation period after hip fracture despite elevated serum level of cortisol also might involve the effect of chronic stress on cortisol sensitivity.

However, acute modulation of GC sensitivity in response to short-term psychosocial stress has only been investigated in a small number of studies. In students, it has been demonstrated that stress associated with academic examinations provokes an activation of the HPA axis with increased levels of cortisol followed by a transient decrease in the cortisol sensitivity of leukocytes ex vivo (24). Similarly, the social stress induced changes in cortisol sensitivity for pro-inflammatory cytokine production by LPS-stimulated whole blood cultures of healthy humans [23]. Moreover, there is also evidence for age-related changes in cortisol sensitivity of different target tissues in human and animal models, with greater sensitivity observed in younger individuals [24].

The rapid development of cortisol resistance observed in the present study could be adaptive for the organism to preserve cell function and prepare the immune system for potential unpredictable danger. However, identification of the mechanisms mediating such a rapid modulation of cortisol sensitivity and their possible consequences remains to be investigated.

LPS-stimulated PBMCs of younger control piglets were much more sensitive to inhibition of the proliferative response by cortisol than cells of piglets at older age [11]. This finding confirms an age-dependent effect, because it was documented that neonatal lymphocytes are more sensitive to cortisol inhibition than are those from older pigs [24].

Production of pro-inflammatory cytokines importantly contributes to host defense against pneumonia. Conversely, while the anti-inflammatory cytokine IL-10 is protective in models of overzealous immune activation, it impairs host defense during pneumonia. Local modulation of the cytokine network may serve as an important addition to antibiotic therapy, especially when faced with multi-drug resistant organisms and/or immunocompromised hosts. Anti-IL-10 protects mice against lethality during pneumococcal pneumonia. Mice were intranasal inoculated with 3x103 CFU Streptococcus pneumonia after intraperitoneal administration of a neutralizing anti-IL-10 mAb or an irrelevant control mAb [13].

Similar results were obtained in studies with experimental pneumonia with Streptococcus pneumoniae. Treatment of mice with recombinant IL-10 resulted in a decrease of lung TNF levels, while administration of an anti-IL-10 antibody resulted in a 31⁄2-fold rise in lung TNF alpha levels. In animals treated with anti-IL-10, bacterial counts from lung and blood were lower and survival was significantly increased. These results indicate that during pneumonia, IL-10 attenuates the pro-inflammatory cytokine response within the lungs, hampers effective clearance of the infection, and shortens survival [13].

Inflammation during pneumonia is orchestrated by locally produced pro-inflammatory and anti-inflammatory cytokines. Important differences exist between the role of cytokines during localized infections and fulminant systemic infections. Whereas excessive production of pro-inflammatory cytokines at the systemic level causes organ failure and death in animal models of fulminant sepsis, the local production of pro-inflammatory cytokines importantly contributes to host defense against pneumonia [13].

The brain and the immune system are functionally linked through neural and humoral pathways, and decreased immune competence with higher incidence of infections has been demonstrated in several acute neurological conditions [15].

A strong cytokine mediated anti-inflammatory response was recently observed in stroke patients at higher risk of infection, although infection could not demonstrate an independent association with the progression of the symptoms. The appearance of infection in patients with acute stroke obeys in part to immunological mechanisms triggered by acute brain injury. An excessive anti-inflammatory response is a key facilitating factor for the development of infection, and it is likely that this immunological response represents an adaptive mechanism to brain ischemia [14].

Contrarily, it is unclear whether infection contributes independently to poor outcome in human stroke. Overall, a better understanding of the cross-talk between the brain and the immune system might lead to more effective therapies in patients with acute stroke.
In summary, this study shows that a single exposure to psychosocial stress and trauma in elderly causes activation of the HPA axis and suppression of circulating TNF alpha. Furthermore, isolation induces a state of cortisol resistance in blood immune cells as increasing inducibility of PBMCs to LPS demonstrates during observation period after hip fracture, which may be an adaptive advantage to maintain cellular immune responses in the short term.

TNFα blocking drugs are used in the treatment of a number of inflammatory conditions. It is likely that the use of these drugs will increase. There have been reports of serious infections with these drugs [25-27]. Doctors need to be aware of the potential for sepsis, especially as they are increasingly likely to encounter patients on anti-TNF drugs. Two cases of life threatening intra-abdominal sepsis in patients with rheumatological conditions receiving anti-TNF drugs are presented [28].

Despite promising preclinical testing and the expenditure of several billion dollars, anti-inflammatory agents designed to inhibit specific host mediators during sepsis failed to show benefit [29].

Our opinion individual therapy is the more safe and more effective. The level of circulating TNF should be measured and the appropriate TNF antibody or soluble receptor should be calculated reaching the reduced TNF level with effective TNF level which is able to protect the host Taken together, host response following hip fracture and other injuries is modified by brain and stress. Determination of serum ACTH, cortisol and TNF as well as inducibility and count of PBMCs can show the subgroups of host responses what may predict outcome of hip fracture. And injuries. Our results indicate the double face behavior of TNF e.g. high production can kill the host; low production is not able to protect the host. The norm regulated host response is the most beneficial.

Acknowledgments
Part of this work was presented at the Surgical Infection Society-Europe Annual Congress, Leon, Spain 2011.

Author Disclosure Statement
No competing financial interests exist.

References
1. Cooper C, Campion G, Melton LJ (1992) Hip fractures in the elderly: a world-wide projection. Osteoporosis Int 2: 285-289.
2. Gomez D, Haas B, Hemmila M, et al. (2010) Hips Can Lie: Impact of Excluding Isolated Hip Fractures on External Benchmarking of Trauma Center Performance J. Trauma 69: 1037-1040.
3. Boxma H, Broekhuizen T, Patka P, Oosting H (1996) Randomized controlled trial of single-dose antibiotic prophylaxis in surgical treatment of closed fractures: the Dutch Trauma Trial Lancet 347: 1133-1137.
4. Klevens RM, Edwards JR, Richards CL Jr, et al. (2007) Estimating health care-associated infections and deaths in U.S. Hospitals, Public Health Rep 122: 160-166.
5. American Thoracic Society; Infectious Diseases Society of America (2005) Guidelines For the management of adults with hospital-acquired, ventilator-associated, and Healthcare-associated pneumonia. Am. J. Respir. Crit. Care Med 171: 388-416.
6. Jurney TH, Cockrell JL Jr, Lindberg JS, et al. (1987) Spectrum of serum cortisol response to ACTH in ICU patients: Correlation with degree of illness and mortality Chest 92: 292-295.
7. Reincke M, Allolio B, Wurth G, et al. (1993) The hypothalamic-pituitary-adrenal axis in critical illness: Response to dexamethasone and corticotropin-releasing hormone. J. Clin. EndocrinolMetab 77: 151-156.
8. Arlt W, Allolio B, Adrenal insufficiency (2003) Lancet 361: 1881-1893.
9. Hinshaw LB, Beller BK, Chang AC, et al. (1985) Corticosteroid/antibiotic treatment of adrenalectomized dogs challenged with lethal E. coli. Circ Shock 16: 265-277.
10. Darlington DN, Chew G, Ha T, et al. (1990) Corticosterone, but not glucose, treatment enables fasted adrenalectomized rats to survive moderate hemorrhage. Endocrinology 127: 766-772.
11. Tuchscherer M, Kanitz E, Puppe B, et.al. (2010) Altered Immunomodulation by Glucocorticoids in Neonatal Pigs Exposed to a Psychosocial Stressor Pediatr. Res 68: 473-478.
12. Strauss J, Aboab J, Rottmann M (2009) Plasma cortisol levels in Guillain-Barre´ syndrome Crit Care Med 37: 2436-2440.
13. Schultz MJA, W. Rijneveld S, JH van Deventer et al. (1999) Cytokines and host defense in pneumonia Intensivmed 36: 270-275.
14. Aisiku IP, Yamal JM, Doshi P, Benoit JS, Gopinath S, et al. (2016) Plasma cytokines IL-6, IL-8, and IL-10 are associated with the development of acute respiratory distress syndrome in patients with severe traumatic brain injury. Critical Care 20: 288.
15. Chamorro A, Urra X, Planas AM (2007) Infection after acute ischemic stroke a manifestation of brain induced immunodepression Stroke 38: 1097-1103.
16. Marik PE, Zaloga GP, (2002) Adrenal Insufficiency in the critically ill: A new look at an old problem. Chest 122: 1784-1796.
17. DeRijk R, Michelson D, Karp B, et al. (1997) Exercise and circadian rhythm-induced variations in plasma cortisol differentially regulate interleukin-1_ (IL-1_), IL-6, and tumor necrosis factor-_ (TNF_) production in humans: high sensitivity of TNF_ and resistance of IL-6. J Clin. Endocrinol. Metab 82: 2182-2191.

18. Rohleder N, Wolf JM, Kirschbaum C (2003) Glucocorticoid sensitivity in human's interindividual differences and acute stress-effects. Stress 6: 207-222.
19. Stark JL, Avitsur R, Padgett DA, et al. (2001) Social stress induces glucocorticoid resistance in macrophages. Am J. Physiol. Regul. Integr. Comp. Physiol 280: R1799-R1805.
20. Avitsur R, Stark JL, Sheridan JF (2001) Social stress induces glucocorticoid resistance in subordinate animals. Horm. Behav 39: 247-257.
21. Merlot E, Moze E, Dantzer R, et al. (2004) Cytokine production by spleen cells after social defeat in mice: activation of T cells and reduced inhibition by glucocorticoids. Stress 7: 55-61.
22. Bauer ME, Vedhara K, Perks P, et al. (2000) Chronic stress in caregivers of dementia patients is associated with reduced lymphocyte sensitivity to glucocorticoids. J Neuroimmunol 103: 84-92.
23. Rohleder N, Schommer NC, Hellhammer DH, et al. (2001) Sex differences in glucocorticoid sensitivity of proinflammatory cytokine production after psychosocial stress. Psychosom. Med 63: 966-972.
24. Kavelaars A, Zijlstra J, Bakker JM, et al. (1995) Increased dexamethasone sensitivity of neonatal leukocytes: different mechanisms of glucocorticoid inhibition of T cell proliferation in adult and neonatal cells. Eur. J. Immunol. 25: 1346-1351.
25. Kroesen S, Widmer A F, Tyndall A, et al. (2003) Serious bacterial infections in patients with rheumatoid arthritis under anti-TNF-alpha therapy. Rheumatology 42: 617-621.
26. Lee J H, Slifman N R, Gershon S K, et al. (2002) Life-threatening histoplasmosis complicating immunotherapy with tumour necrosis factor alpha antagonists infliximab and etanercept. Arthritis Rheum 46: 2565-2570.
27. Slifman N R, Gershon S K, Lee J - H. et al. (2003) Listeria monocytogenes infection as a complication of treatment with tumor necrosis factor alpha-neutralizing agents. Arthritis Rheum 48: 319-324.
28. Yang WC, Schultz RD (1986) Effects of corticosteroid on porcine leukocytes: age-related effects of corticosteroid inhibition on porcine lymphocyte responses to mitogens. Vet. Immunol. Immunopathol 13: 19-29.
29. Eichacker P Q, Parent C, Kalil A, Esposito C, Cui X, et al. (2002) Risk and theefficacy of antiinflammatoryagents: Retrospective and confirmatorystudies of sepsis. American Journal of Respiratory and Critical Care Medicine 166: 1197-1205.