Systemic inflammatory response syndrome (SIRS) in Mosul: Clinical characteristics and predictors of poor outcome

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ABSTRACT

Objectives: Systemic inflammatory response syndrome is one of the most important causes of intensive care unit (ICU) morbidity and mortality worldwide. The aim of this study is to explore the spectrum of diseases responsible for SIRS admission in Mosul, and to identify the mortality rate and the factors associated with poor outcome.

Methods: Fifty patients with sepsis or non-infective SIRS were studied during the period from June 1st to November 30th 2009. Patients were collected from the medical ICU and the general medical wards in Ibn-Sina Teaching Hospital in Mosul,. Acute physiology and chronic health evaluation II (APACHE II) score was utilized to assess the severity of illness on admission. The patients included in the study received the standard medical care according to their condition, and were followed to delineate the cause of their illness, the percentage of microbiological confirmation, the duration of hospital stay, the mortality rate and the factors that influence their outcome.

Results: Sepsis represented 86% of cases of SIRS, of which 82% of them were caused by community acquired infections. Pneumonia was responsible for 48.8% of sepsis cases, followed by acute pyelonephritis and intra-abdominal infection. Sepsis was microbiologically confirmed in 44.2% of patients, and blood culture was positive in 18.6% of patients. Impaired consciousness, anaemia, hyperglycaemia and high blood urea were associated with excess mortality rate; while positive blood culture and hypoalbuminaemia correlated with high APACHE II score. The overall mortality rate was 44%. Patients with severe sepsis had a mortality rate of 55.2%.

Conclusion: SIRS is an important cause of hospital admission in Mosul, with associated high mortality rate. ICU admission should be seriously considered for patients with certain risk factors that predict poor outcome.

الخلاصة

الأهداف: متلازمة الاستجابة الالتهابية المجموعية (وبضمنها الإنتان) واحدة من أهم أسباب المراضة والوفيات في وحدات العناية المركزة في العالم أجمع. الهدف من هذه الدراسة التحري عن طيف الأمراض المسببة لمتلازمة الاستجابة الالتهابية المجموعية في الموصل وتحديد نسبة الوفيات والعوامل المقترنة بالحصيلة السيئة.

طرق العمل: تمت دراسة خمسين مريضا مصابا بالإنتان أو الحالات غير المعدية من متلازمة الاستجابة الالتهابية المجموعية في الفترة بين ١ حزيران و ٣٠ تشرين الثاني ٢٠٠٩. تم جمع المرضى من وحدة العناية المركزة الباطنية وأجنحة الباطنية العامة في مستشفى ابن سينا التعليمي في الموصل. استخدم حرز (أباشي ٢) لتحديد شدة الاعتلال عند الإدخال. خضع المرضى للعناية الطبية القياسية كل حسن حالته، وتم تعقبهم لتحديد سبب مرضهم ونسبة الإثبات المايكرو بيولوجي وفترة بقائهم في المستشفى ونسبة الوفيات والعوامل المؤثرة في حصيلة حالتهم.

النتائج: مثل الإنتان ٨٦٪ من حالات متلازمة الاستجابة الالتهابية المجموعية، كان ٨٣٪ منهم حالات عدوى مكتسبة في المجتمع. كان الالتهاب الرئوي هو المسبب لـ ٤٨,٨٪ من حالات الإنتان، يليه التهاب الحويض والكلية الحاد والأمراض

المعدية داخل البطن. تم إثبات الإنتان مايكرو بيولوجيا في ٤٤,٢٪ من المرضى وكان زرع الدم موجبا في ١٨,٦٪ من المرضى. ظهر اعتلال الوعي وفقر الدم وفرط سكر الدم وارتفاع نسبة اليوريا فيه عوامل مقترنة بزيادة نسبة الوفيات، بينما نتيجة زرع الدم الموجبة ونقص ألبومين الدم مرتبطتان بارتفاع حرز أباشي. نسبة الوفاة الإجمالية كانت ٤٤٪، ووفيات المرضى المصابين بإنتان شديد ٥٥,٢٪.

الاستنتاج: متلازمة الاستجابة الالتهابية المجموعية سبب مهم لدخول المستشفى في الموصل مقترن بنسبة وفيات عالية. يجب النظر بجدية إلى إدخال المرضى الذين لديهم عوامل اختطار معينة تنبئ بحصيلة سيئة إلى العناية المركزة.

Localized inflammation is a physiological protective response which is generally tightly controlled at the site of the injury. Loss of this local control results in an exaggerated systemic response which is clinically identified as systemic inflammatory response syndrome (SIRS). SIRS may be initiated by infection or by non-infectious causes such as trauma, autoimmune reactions, malignancy, cirrhosis and pancreatitis [(1)]. SIRS associated with suspected or proved infection is called sepsis. Morbidity and mortality of sepsis remain unacceptably high. It is still one of the most prevalent causes of intensive care units (ICU) morbidity and mortality worldwide [(2,3)], with as many deaths annually as those of myocardial infarction[(4)].

In 1991, in an attempt to stratify the spectrum of sepsis, a consensus conference organized by the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) was held in USA to clinically define the terms: SIRS, sepsis, severe sepsis, septic shock and multiple organ dysfunction syndrome (MODS). To meet the definition of sepsis, patients need to satisfy at least two out of four SIRS criteria, in association with having a suspected or confirmed infection [(5)].

The aim of this study is to identify the spectrum of diseases which are responsible for SIRS admission in a medical ICU and the general medical ward in Mosul. We intended to study the severity of illness, the requirement for ventilator therapy, the overall mortality and the factors associated with poor outcome. The study utilized the definitions adopted by the 1992 statement of the ACCP/SCCM consensus conference (which was retained by the 2001 international sepses definition conference) [(6)].

Patients and methods

Fifty patients were studied prospectively; they were collected from the medical ICU and the general medical wards in Ibn-Sina Teaching Hospital in Mosul during the period from 1st June to 30th November 2009.

Patients were included in the study if they met the diagnostic criteria of SIRS according to the definitions given by the ACCP/SCCM consensus conference. Accordingly, included patients should have two or more of the following criteria:

1- Temperature >38 °C or <36°C.
2- Heart rate >90 beats/minute.
3- Respiratory rate >20 breaths/minute.
4- White blood cell count >12000 cell/μl or <4000 cell/μl or >10% immature bands.

Patients included in the study were systematically evaluated. Careful history taking included the details of current symptoms and associated co-morbidities. Enquiry was made regarding occupation, residence and past medical or surgical events. The patients were classified as having either community acquired or hospital acquired illness (those who developed their illness while admitted for other conditions or had been referred from other medical, surgical or obstetric and gynaecological departments after developing the acute illness in their original wards). Patients guaranteed for the suspicion of infection with H1N1 influenza were excluded; as well those less than 10 years old, or those who have stayed less than 24 hours in hospital.

The acute physiology and chronic health evaluation II (APACHE II) score was calculated for every patient. This is the most widely used scoring system to assess the severity of illness and the excepted mortality of

critically ill patients. The score utilizes the worst values of 12 physiological variables during the first 24 hours following admission, along with an evaluation of the patient's chronic health prior to admission [7].

The following laboratory investigations were done routinely (and repeated when necessary):

1- Complete blood picture including platelet count, blood film and erythrocyte sedimentation rate (ESR).
2- Prothrombin time (with the International Normalized Ratio (INR)) and activated partial thromboplastin time.
3- Serum sugar, urea and creatinine.
4- Serum sodium, potassium and calcium.
5- Liver function tests (serum bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and albumin).
6- General urine examination.
7- Blood culture.

Additional investigations were ordered according to the requirements for the individual cases; these included:

1- Other biochemical investigations like serum amylase.
2- Hepatitis viral serology.
3- Sputum Gram stain, Ziehl-Neelsen stain and culture.
4- Urine culture.
5- Pleural fluid analysis and culture.
6- Cerebrospinal fluid examination and culture.
7- Wound or ulcer swab and culture.

Chest x-ray was the only imaging which was done as a routine. Ultrasound examination of the abdomen was done for most patients. Few patients had CT-scan, and to a lesser extent, magnetic resonance imaging.

Patients were considered to have an infection if this was microbiologically documented or at least clinically suspected requiring evidence such as the presence of white blood cells in a normally sterile body fluid, acutely inflamed abdominal organ, chest x-ray consistent with pneumonia or a clinical syndrome associated with high probability of infection [6,8].

Septic shock was defined as acute circulatory failure characterized by persistent arterial hypotension unexplained by other causes. Hypotension was defined by a systolic blood pressure <90 mmHg; mean arterial pressure <60, or a reduction in systolic blood pressure of more than 40 mmHg from baseline, despite adequate volume resuscitation, in the absence of other causes of hypotension. MODS were considered to be a dysfunction of more than one of the above organs, requiring intervention to maintain homeostasis [6].

The source of sepsis and the cause of the non-infective SIRS were determined, and daily follow up was made to record the last stage of sepsis reached, the duration of hospital stay and the final outcome (survival or death).

All variables were expressed as numbers and percentages and were compared with unpaired T-test, ANOVA test, Fisher Freeman Halton test, Fisher Exact test and Chi-square test. The analysis was conducted using the SPSS package 16, p-value <0.05 was considered statistically significant and p-value <0.001 was considered highly significant.

Results

Fifty consecutive patients with SIRS were included in the study. Their age ranged from 12 to 89 years, with mean of 41.52 ± 20.53 years. Twenty six of them were males (52%) and twenty four were females (48%). Their mean duration of illness prior to admission was 7.43 ± 6.68 days.

Sepsis represented the major cause of SIRS in our study (43 patients (86%)), while non-infective SIRS was found in 7 patients (14%). Pneumonia was the leading cause of sepsis in our series; responsible for 21 (48.8%) cases, four of them were nosocomial. Acute pyelonephritis, intra-abdominal, and central nervous system infections were responsible for four cases each (8%). Two patients (4%) were found to have infective endocarditis. Although sepsis was suspected, the source of infection was not established in 3 patients. Community acquired sepsis represented (82%) of cases, the remainder (18%) were hospital acquired. There was no statistically significant difference regarding the severity of illness (assessed by APACHE II score) or mortality between

hospital and community acquired cases. Four of seven patients with non-infective SIRS were found to have disseminated malignant diseases (carcinoma of the breast, prostate, teratoma and acute leukemia). Two patients had acute pancreatitis and a woman was diagnosed with active systemic lupus erythematosus (Table 1).

Sepsis was bacteriologically confirmed in 19 patients (44.2%). Confirmation was based on a positive blood culture in 8 patients (18.6% of all sepsis cases), sputum culture in 6 patients, CSF, pleural fluid, ulcer swab, urine and stool culture in one patient each. In the remaining 24 patients (55.8%), sepsis was suspected clinically, supported by laboratory and imaging results. There was no statistically significant difference between patients with positive and negative blood culture results in relation to APACHE II score, days of stay in hospital or mortality. However, patients with positive blood culture reached higher stage of illness (septic shock or MODS) when compared with those of negative blood culture (p=0.217).

The diagnosis of SIRS was based on two diagnostic criteria in 19 patients (38%), three criteria in 18 patients (36%) and the whole four criteria in 13 patients (26%). The increasing number of diagnostic criteria on which the diagnosis of SIRS was made was strongly associated with more advanced stage of illness (p<0.001) and higher mortality (p=0.0097).

An even stronger association was found between the level of consciousness assessed by Glasgow Coma Scale (GCS) and the subsequent stage of SIRS reached and the mortality rate. Patients with an initially reduced consciousness (GCS of 14 or less) reached higher stage of illness (more commonly passed to septic shock and MODS), and had higher mortality (77.3% versus 22.7%) compared with those having normal GCS on admission (p<0.001) (Table 2).

Anaemia was present in 22 patients (44%). These patients had significantly higher mortality than non anaemic patients (68.2% versus 31.8%, p>0.001). On the other hand, elevated ESR had no significant effect on the APACHE II score (p=0.115) or mortality rate (p=0.243), even when reached a level exceeding 70 mm/hr.

Hyperglycemia, defined as fasting blood sugar ≥7.8 mmol/l, had developed in 17 patients (34%); of whom 10 (58.8%) were non diabetic before their current illness (stress hyperglycemia). Patients with hyperglycemia had significantly higher APACHE II score (p=0.006), longer stay in hospital (p=0.029) and more advanced stage of SIRS (p=0.0109) (Table3). The mortality rate of these patients (58.8%) was higher than those who remained normoglycemic (36.4%) (p<0.001). Elevated serum urea (>7 mmol/l), rather than creatinine was associated with excess mortality rate (77.3% in those having high blood urea on admission, compared with 22.7% in patients with normal levels) (p=0.014).

Serum albumin level correlated significantly with the APACHE II score; the highest scores were encountered in those with serum albumin below 30gm/l (p= 0.007), and these patients reached more advanced stages of septic shock and MODS compared with those having normal serum albumin levels (p<0.001). There was also a non significant association between hypoalbuminaemia and a higher mortality rate and a longer stay in hospital (p=0.101 and p=0.301 respectively) (Table 4).

Overall, the most common organ dysfunction noticed in our study was related to the central nervous system (36% of cases), followed by the cardiovascular system (30%), kidneys (28%), liver (28%), lung (22%) and blood (10%). Two of our patients were already on ventilator therapy for respiratory paralysis caused by Guillain Barre syndrome before the development of sepsis (ventilator associated pneumonia). Eight patients (16%) required ventilator therapy to treat ARDS, or to support comatose patients. APACHE II score showed a very significant association with the stage of SIRS reached and mortality rate (p<0.001 for each).

The in-hospital mortality rate of our group of patients was (44%). Patients with sepsis had a mortality rate of 39.5%, while patients with non-infective SIRS had 71.4% mortality. This difference did not reach statistical significance (p=0.122). Nine patients (18%) had sepsis,

which did not progress further; one of them only died (mortality rate of 11.1%). Twenty patients (40%) reached a stage of severe sepsis (without further progression); of whom four died (mortality rate of 20%). Septic shock and MODS complicated severe sepsis in 6(12%) and 15(30%) of patients; their mortality rate were 50% and 93.3% respectively. Overall, the mortality rate of all patients who reached severe sepsis was 51.2%.

Twenty four of our patients were in the ICU (48%), and 26 were in the general medical wards (52%). Despite a higher mean APACHE II score (22.8 versus 15.2) and a more advanced stage of SIRS among patients admitted to the ICU, there was no significant difference in the mortality rate between the two groups (p=0.802). All ventilated patients were in the ICU.

Table (1): Causes of sepsis and non-sepsis SIRS.

Causes of sepsis	No.	Causes of SIRS	No.
Pneumonia/Total Nosocomial pneumonia Empyema Complicating measles Others	21 4 1 1 15	Disseminated malignancy/Total Carcinoma of breast (lymphangitis carcinomatosis) Leukemic meningitis Carcinoma of prostate (cerebral metastasis) Teratoma	4 1 1 1 1
Intra-abdominal infection/Total Acute cholecystitis Liver abscess Pelvic abscess Perforated acute appendicitis	4 1 1 1 1	Acute pancreatitis	2
Acute pyelonephritis	4	Autoimmune disease (SLE with lupus nephritis and cerebritis)	1
CNS infections/ Total Encephalitis Pyogenic meningitis Neurobrucellosis	4 2 1 1		
Infective endocarditis	2		
Skin and soft tissue infection/Total Infected decubitus ulcer Cellulitis	2 1 1		
Others/Total Primary staphylococcal septicemia Shigellosis Suppurative lymphadenitis	3 1 1 1		
Unknown cause	3		
Total	43		7

Table (2): The association of Glasgow Coma Scale with the severity of sepsis and outcome.

GCS / Stage of illness	Normal		Low		p-value
	No.	%	No.	%	
SIRS/sepsis	9	100	0	0.0	<0.001
Severe SIRS/severe sepsis	12	60.0	8	40.0	
Septic Shock	2	33.3	4	66.7	
MODS	1	6.7	14	93.3	
Total	24	48.0	26	52.0	
Mortality / GCS	**Dead**		**Alive**		**p-value**
	No.	%	No.	%	
Normal	5	22.7	19	67.9	<0.001
Low	17	77.3	9	32.1	
Total	22	100	28	100	

Table (3): The association of blood glucose level with the severity of sepsis and outcome.

Blood glucose / Stage of illness	<7.8		≥7.8		p-value
	No.	%	No.	%	
SIRS/sepsis	7	21.2	2	11.8	0.0109
Severe SIRS/severe sepsis	13	39.4	7	41.2	
Septic Shock	5	15.2	1	5.9	
MODS	8	24.2	7	41.2	
Total	33	100	17	100	
Mortality / Blood glucose	Dead		Alive		p-value
	No.	%	No.	%	
<7.8	12	54.54	21	75	<0.001
≥7.8	10	45.45	7	25	
Total	22	44.0	28	56.0	

Table (4): The association of serum albumin with the severity of sepsis and outcome.

Serum albumin (g/l) / Stage of illness	Normal		<36		<30		p-value
	No.	%	No.	%	No.	%	
SIRS/sepsis	6	33.4	2	10.5	1	7.7	<0.001
Severe SIRS/ severe sepsis	9	50.0	9	47.4	2	15.4	
Septic Shock	0	0.0	5	26.3	1	7.7	
MODS	3	16.6	3	15.8	9	69.2	
Total	18	100	19	100	13	100	
Serum albumin (g/l) / Mortality	Normal		<36		<30		p-value
	No.	%	No.	%	No.	%	
Dead	6	33.3	7	36.8	9	69.2	0.101(NS)
Alive	12	66.7	12	63.2	4	30.8	
Total	18	100	19	100	13	100	

Discussion

Sepsis represented the majority of cases of SIRS in this study (86% of cases). Hernándes et al noticed a similar proportion. They diagnosed sepsis in 79% of their patients, with the remaining 23% had non-infective SIRS [9]. Sepsis was hospital acquired in 18% of cases only. Such cases constituted a much higher percentage in a recent Spanish study (49.5%) [8]. The lower impact of hospital acquired infections reflects the under use of instrumentation (including intravenous catheterization and mechanical ventilation) in our hospital.

Pneumonia was the commonest cause of sepsis in both community and hospital acquired cases in our study (48.8%). Almost all recent studies in the field found the lungs (pneumonia) the major source of sepsis [4,8,10-14]; this ranged from a percentage of 40% in a large multicentre trial in USA [4] to 86% in a pan-European study published in 2006 [10]. The only notable exception was a recent Mexican study, where abdominal infection predominated over pulmonary infection [15]. Abdominal and urinary tract infections were the second and third causes of sepsis in our study, shared by most other similar studies [8, 10, 12-14].

Sepsis was more frequently suspected than microbiologically documented. Periera et al from Portugal had a similar percentage of culture proven cases [14](39% compared with 44% in our study). However in three other larger studies, 60% – 64% of sepsis cases were microbiologically documented [8,10,16]. It seems that over-reliance on empirical therapy in our centre has largely replaced a thorough and careful search for microbiological confirmation.

Blood culture was positive in 18.6% of cases; a percentage quite similar to two other studies conducted by Rangel-Frausto et al [17](17%) and Pereira [14](20%), and a little less than the results of Selberge et al [18] (30%) who tried their best to differentiate sepsis cases from non-infective SIRS in order to compare certain biochemical markers. The low percentage of positive blood culture in general reflect the fact that sepsis does not indicate the presence of viable bacteria in the bloodstream, but rather an uncontained inflammatory response to infection. Moreover, many patients had received frequent courses of antibiotics before being admitted as sepsis (which reduces the chance of positive blood culture) and infections caused by non bacterial pathogens are undetectable by standard cultures. Variation in the number of blood culture positive cases in different studies is also influenced by the location of infection. For example, peritoneal infection results in a more frequent release of bacteria to the circulation compared with pulmonary infection [18].

Positive blood culture was associated with higher prevalence of septic shock and MODS. Rangel-Frausto et al found a stepwise increase in the percentage of positive blood culture with increasing stage of sepsis (17%, 25% and 69% for severe sepsis, septic shock and MODS, respectively) [17]. Two multi-centre trials in Portugal [14] and France [16] found bacteraemia (manifested by positive blood culture) a risk factor for early mortality. Despite the higher mortality rate in blood culture positive patients in our study (75% Vs 38%), the small sample size did not mount a statistical significance.

The increasing number of diagnostic criteria on which the diagnosis of SIRS was made strongly correlates with more advanced stage of illness and higher mortality. Sprung et al found that fulfilling more than two criteria carries a higher risk of subsequent development of severe sepsis, septic shock and MODS [19]. This finding was confirmed by Rangel-Frausto et al who stated that "SIRS with only two criteria – as initially proposed – is less helpful in defining a subset of ICU and ward patients who are at especially high risk of severe sepsis than SIRS with three or all four criteria" [17]

Our findings regarding anaemia in sepsis patients is consistent with the accumulating evidence that anaemia in critically ill patients is common and correlates with poor outcome [20,21]. The mechanism of anaemia in these patients is similar to that of chronic disease anaemia, except that the onset is generally rapid [21]. Despite the deleterious effect of anaemia of critical illness, aggressive treatment with blood products can be as detrimental as no treatment with associated increase in morbidity and mortality [21,22]. The use of erythropoietin stimulating agents is rapidly gaining acceptance as a substitute to transfusion therapy [22].

High ESR had no relation with severity of illness assessed by APACHE II score or mortality. This could be due to the fact that ESR is a crude indirect measure of acute phase response. Even an ESR higher than 70 ml/hr was not found a poor outcome index in these patients.

Acute hyperglycaemia is frequently present in situations of stress in both diabetic and non-diabetic patients [23.24]. The prevalence of hyperglycaemia in critically ill patients depends on the defining criteria. In one study conducted in a medical ICU, admission blood glucose above 11.1mmol/L was present in 23% of patients [25]. In another study, conducted in a surgical ICU, admission glucose level was >6.1mmol/L in 86%, almost all of patients became hyperglycaemic during ICU stay [26]. Applying our definition of 7.8 mmol/L, a prevalence of 34% in our study is almost similar.

The strong association between ICU hyperglycaemia and excess morbidity and mortality noticed in our study was also shown by similar studies. Van der Berghe et al reported dramatic (42%) relative reduction in mortality in a surgical ICU when blood glucose was normalized to 4.4 – 6.1 mmol/L by means of insulin infusion (compared with 10 – 11.1 mmol/L in the control group) [26]. The benefit of glucose reduction in the medical ICU was less certain [27.28].

The adverse effect of hypoalbuminaemia in acute illness has been confirmed in a meta-analysis. Hypoalbuminaemia was found a potent and dose dependant predictor of mortality, independent of nutritional status or inflammation. Each 10 gm/L decline in serum albumin concentration significantly raises the odd ratio of mortality by 137%, morbidity by 84% and ICU stay by 28% [29]. However, the use of albumin for volume resuscitation of critically ill patients with serum albumin concentration ≤ 25 gm/L was not associated with reduction of mortality, duration of ICU stay or mechanical ventilation [30,31]. A potential beneficial role of albumin in patients with sepsis requires further study [31]. The association of low serum albumin with disease severity was clearly shown in our study, but significant correlation with mortality rate and hospital stay has not been reached, perhaps because of small sample size.

The overall mortality rate of sepsis in our study was somewhat high (39.5%). In recent epidemiological studies, the mortality rate of sepsis has ranged from 9% [17] to 48.2% [13]. In the above mentioned pan-European study [10], wide variation in mortality of severe sepsis has been noticed in different centres around Europe; being lowest in Switzerland (10%) and highest in Portugal (64%). In comparison, our result of 51.2% mortality rate of these patients seems acceptable.

Despite the more advanced stage of SIRS reached, and the higher mean APACHE II score of our ICU patients compared with those in the general medical wards, there was no significant difference in mortality between these two groups. This result was in agreement with Guidet et al, who found a mortality rate of 49% in severe sepsis patients in the general medical wards and 42% in ICU patients [32]. Blanco et al showed a mortality rate 55% in septic patients in the general wards and 48% in the ICU [8]. The similar mortality rate (despite less severe illness of SIRS patients who remained on the general wards) calls for serious consideration of ICU admission for most cases of SIRS, especially for those who develop severe sepsis.

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