SEVERE, EXTENSIVE, SOFT TISSUE INFECTIONS

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ABSTRACT

We reviewed a number of eight patients treated in for severe perineal and/or abdominal wall extensive infections. Regardless of the origin of infection, all patients presented clinical signs of severe sepsis or septic shock. Successful treatment is conditioned by appropriate intensive care, associated with aggressive surgery. The comparison of our results with previous studies shows that changing the treatment attitude would lead to drastic improvement in mortality.
Key Words: soft tissue infections, severe sepsis/septic shock.

INTRODUCTION

Soft tissue infections are fairly common in surgery and the vast majority need only surgical ambulatory treatment and no antibiotics. Among them some infections require more attention like the diabetic foot, lower limb vascular gangrene, peri anal abscesses, limb phlegmonas; those need special medical and surgical attention, and adequate antibiotic therapy but basically are not life threatening. Finally, among these, there are some cases of life threatening soft tissue infections. In these cases severe sepsis or septic shock are present, due to the aggressive nature of the bacteria involved, and more important, due to the poor status of the patient, caused by associated illness and to the lateness of treatment. Such cases are the real challenge, success being the result of joint effort of ICU doctors and surgeons.

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DEFINITIONS [1]

• SIRS – Systemic Inflammatory Response Syndrome – is defined as systemic response to a variety of severe clinical disturbances and includes 2 or more of the subsequent:

- Temperature < 36^0C or > 38^0C
- Heart rate > 90/min
- Respiratory rate > 20/min or PaO2 < 32 torr
- White blood cells > 12 000/mmc or < 4000/mmc, or > 10% immature elements.

• Sepsis – SIRS due to infection

• Severe Sepsis – Sepsis + organic dysfunction, hypo perfusion/hypotension, oliguria, lactic acidosis, mental status alteration.

• Septic Shock – severe sepsis with hypotension refractory to volemic replenishment.

MATERIAL AND METHOD

Our review includes a number of 34 patients with extensive infections of the perineal area or abdominal wall, perineal abscess, necrotizing fasceitis, lower limb gangrene, admitted in the III-rd Surgery Clinic, Timis County Hospital, between 1993-2002. The criteria for selection included the presence of soft tissue infection and sepsis or septic shock as defined above. Patients with acute peritonitis were not included. Eight patients fulfilled our selection criteria and were included in the study; of these, 4 most significant are presented as case reports.

SIGNIFICANT CASE REPORTS

Case 1 (first case successfully treated): male, 44 years old, 89 kg. **Diagnosis**: Extensive perineal gangrene, secondary to a left perineal abscess. Septic shock.

Local examination: Left perirectal abscess extending to anterior perineum, to the scrotum and further more to left from through the inguinal canal.

Treatment: Fluid replacement was started using normal saline solution, 3000 ml/3 hours. Antibiotics (Cefamandol 1g iv Q 12h + Gentamicin 0,080 g iv Q 12 h, + Metronidazol 1g iv Q 12 h).

Surgery: Under general i.v. anesthesia - excision of necrotic skin and fatty tissue, on the left side of the anal canal and rectum, and incision and drainage of the scrotum.

Programmed surgery: 12 consecutive daily excisions of the necrotic tissue under general anesthesia, saline solution scrubbing and dressing. The right testis was lost due to an iatrogenic vascular lesion; left inguinotomy and Penrose drainage.

Complications: Pseudomonas Aeruginossa was cultured from the surface of the wound, without systemic symptoms. Upper digestive hemorrhage due to benign gastric ulceration; a gastric resection was performed with good recovery.

Outcome: The perineal wound had a good evolution with secondary closure, and the left testis was included into the perineal tissues, the scrotum being virtually absent. The patient was discharged on the 64th day. NB: after 6 months local examination revealed a fully developed "neoscrotum", containing the remaining testis.

Case 7 (first to receive de-escalation therapy): male, CN 16895/2002, 56 years, 176cm, 85 kg. **Diagnosis**: Left colon perforated diverticulitis. Acute retroperitonitis. Abdominal wall gangrene. III-rd degree obesity. IIB Diabetes Mellitus. Septic shock

Local examination reveals a tender tumefaction of the left side with intense swelling of the skin, and subcutaneous gaseous crepit. No signs, clinical or X-ray, of bowel obstruction.

Treatment: Volume replacement (i.v. saline, 4000 ml), gastric aspirate, oxygen therapy, antibiotics (imipenem-cilastatin iv 0.500 g Q 8 h, for 5 days; antibiogram revealed E.Coli + Proteus + Enterobacter, responsive to ceftriaxone, pefloxacine so we changed to ceftriaxon iv 1g Q 8 h + pefloxacin iv 0.200g Q 12 h, 7 days, and ceftriaxon 1 g Q 12h for another 5 days), analgesics.

Surgery: Large debridement incision in the left lower quadrant, opening the inguinal canal, extended upwards, up to the ribs, on the left flank and into the retroperitoneum, posterior to the descending colon, and then towards the pancreatic area. The peritoneal cavity was not opened. A large amount of fetid puss was drained. Soft tissues were moistening with puss and gas. Fat was generously excised, along with some muscles and skin. Aggressive, continuous toilette with saline was performed. Multiple continuous aspirate drainage were installed.

Programmed surgery: Daily, general anesthesia debridment performed, for 7 days; from the second day, the puss rapidly transforms into faces, strongly suggesting a large bowel fistula. This, later, slowly diminished to disappearance until the wound was rapidly covered with granulation tissue

Outcome: The patient healed and was discharged after 56 days. Six months later the patient was operated for a large incisional hernia, and mesh reconstruction of the abdominal wall was performed.

Table 1. Patients with extensive soft tissur infections and severe sepsis or septic shock. Demographic and clinical data

Case No.	1	2	3	4	5	6	7	8
Sex	M	M	M	F	F	F	M	M
Age	44	5	16	56	61	58	56	35
Severe sepsis	+	+	-	-	+	+	-	+
Septic shock	-	-	+	+	-	-	+	-
Obesity	**+**	**-**	**-**	**-**	**+**	**+**	**+**	**+**
Diabetes. Mellitus	-	-	-	+	+	+	+	-
High Blood Pressure	**-**	**-**	**-**	**-**	**-**	**+**	**+**	**-**
Coronary Disease	-	-	-	-	+	+	+	-
Complications	UDH	-	-	MOSF	-	Sacral	-	-
	NI	-	NI	-	-	Escare	-	-
Days before treatment	**6**	**-**	**3***	**7**	**4**	**5**	**5**	**5**
Programmed Surgery	12	26	10	5	8	7	10	9
Hospitalization	**64**	**72**	**45**	**5****	**45**	**48**	**56**	**24**
Outcome	9	7	8	1	9	6***	8	9

Outcome on a 1-10 scale (10 being most satisfactory)
UDH - upper digestive hemorrhage; NI - nososcomial infection; MOSF - multiple organ and system failure;
*- transferred from another hospital; **- deceased on the 5-th day; *** - patient reoperated for recurrent incisional hernia 9 months later.

Table 2. Selection criteria

Criteria/Case No.	1	2	3	4**	5	6	7	8
Age	44	5	16	56	61	58	56	35
Sex	M	M	M	F	F	F	M	M
SEPSIS	YES	NO*/YES	YES	YES	YES	YES	YES	YES
t>38	38	36	38,6	38,5	38	37	38	37
HR>90	120	125	100	120	100	110	105	120
RR>20	24	25	22	24	22	22	20	21
PaO2<32 torr	NO	NO*	YES	YES	NO	YES	YES	NO
WBC>12000	YES	NO*	YES	#	YES	YES	YES	YES
WBC<4000	#	NO*/YES	#	YES	#	#	#	#
Lactic acid	#	YES	#	#	#	YES	#	YES
hypotension	YES	YES	YES	YES	NO	NO	YES	YES
Oliguria	YES	YES	YES	YES	YES	YES	YES	NO
Mental status altered	YES	YES	YES	YES	YES	YES	YES	NO
refractory hypotension	YES	NO*	NO	YES	NO	NO	YES	NO
SIRS								
SEVERE SEPSIS		4-th day						
SEPTIC SHOCK								

* even if initially there were only signs of SIRS, he later developed SEVERE SEPSIS
** patient died on the 5-th day

RESULTS

Aggressive surgical treatment led to excellent results, only one of eight patients being lost. Earlier studies (a study done on 4 patients between 1987-1990) suggested severe evolution, with poor results, three of four patients being lost. However, long hospitalization and high costs are the downside.

Table 3. Surgery and programmed surgery

Case No	Re-operations general anesthesia	Days AB treatment Initial+changed	Hospitalization days
1	12	4+10=14	64
2	26	5+21=26	42
3	10	14+7=21	45
4	5	5	5 /deceased
5	7	4+10=14	45
6	8	4+10=14	48
7	7	3+7=10	56
8	14	4+10=14	24

DISCUSSIONS

In all cases, poor general status and clinical signs of sepsis are dominant. In some cases they were so overwhelming, that the examining physician in the ER, overlooked the local sign of infection. Basically, the patients (Tab. 1) are confuse, sleepy, disoriented and in some cases comatose; hyperventilation is present (RR> 20/min), cyanosis might be present, as SaO_2 < 90%, in 1/3 of cases. Patients are hypovolemic, hypotensive (< 90 mmHg), tachicardic, oliguric or anuric, there is a delay in capillary plasma refill > 3-4 sec. Body core temperature is in most cases decreased despite sepsis. Blood sugar levels are elevated 120-160 mg%.

At first sight local examination might not reveal the true extent of the infection, since the skin is relatively resistant to ischemia due to subjacent infection of fat tissue, but the usual signs of inflammation are present. Local destruction of the skin and fatty tissues is often "breath taking", necrosis of the skin, fat, fascia, muscles, is extensive and "shocking".

Sadly, in most cases, anamnesis would reveal that the present disease started with rather benign infections, which were overlooked or inadequately treated.

Obesity, diabetes mellitus, high blood pressure/ coronary disease, are usually present.

Antibiograms reveal comunitary germs, Gram negative (Klebsiella, E.Coli, Proteus), in some cases anaerobes (Enterococus, Bacteroides), and Gram positive (MSSA – methicillin sensitive Staphilococus Aureus) with "normal", initial, susceptibility to antibiotics.[2,3]

The key to successful treatment is appropriate intensive care associated with aggressive surgery.

Intensive Care treatment

Volume replacement

Patients must be admitted and treated in ICU prior to surgery. Volemic corrections: at least 2 peripheral venous lines; NaCl 0,9% or Ringer is delivered at high rate until the urine output is at least 0,5-0,7 ml/kg/ min, or CVP is 12-14 cm H_2O (monitoring the Central Venous Pressure is to be considered when there is a suspicion of chronic renal failure and/or heart failure). Usage of plasma expanders will not improve morbidity or mortality.[4] Even if on short term they ensure rapid

Table 4. Antibiotic treatment

Case No.	Culture	Empiric AB Initial	AB according to Antibiogram	Initial Success
1	E.Coli+ Bacteroides	Cefamandol+Genta +Metronidazol		Yes +/-
2	Pasturella Sp+ MSSA	Penicilin+Genta +Metronidazol	Ceftriaxon	NO
3	Pseudomonas Aeruginosa***	Ceftriaxon+Genta +Metronidazol	Pefloxacin+ Gentamicin	NO
4	Streptococus+ Clostridium	Cefoperazon+Genta +Metro+Pefloxacin		YES+/- deceased
5	E. Coli+ Bacteroides	Cefamandol+Genta +Metronidazol	Augmentin + Ciprofloxacin	NO
6	E.Coli +Klebsiella Proteus	Cefamandol+Genta +Metronidazol	Augmentin+ Pefloxacin	NO
7	E.Coli + Proteus+ Enterobacter	Imipenem	Ceftriaxon+ Pefloxacin	YES
8	MSSA	Ceftriaxon+Genta +Metronidazol	Ciprofloxacin+ Genta	NO

*** - NOSOCOMIAL INFECTION : patient transferred from another hospital; positive hemoculture on arrival.

plasma refill, on long term they might affect extra vascular restore of sodium and water.

Specific treatment of associated disease is concomittant.

Antibiotics: "Getting it right the first time"

Although dealing with communitary germs (Tab. 4), our oppinion is that they should not be treated as common communitary infections but rather as severe infections. This is mainly because the hosts are immunodepresed, due to associated disease delayed treatment, and severe sepsis/septic shock.[6] This demands an appropriate antibiotic treatment from the start. The de-escalation therapy can be a feasible solution.

Escalation therapy .The initial AB treatment, in 7 cases (1, 2, 3, 4, 5, 6 and 8) was a classic escalation therapy: "empiric treatment", started using a Cephalosporin (II-nd and later III-rd generation), + aminoglicosides (gentamicin/netilmycin), + imidazoles (metronidazol), and later escalated to an antibiotic combination according to the antibiogram. As seen in Table 3 this escalation therapy was efficient only in 1 case (case 1), and in one case the initial empiric therapy was correct but the patient died due to MSOF (case 5). In the other 5 cases (2, 3, 4, 6,and 8) the initial empiric treatment proved later to be incorrect, and the antibiotic combination was changed according to the antibiogram. This means that 3 to 5 day of antibiotic treatment (until the results for antibiotic sensibility), were "lost"; in those cases the correct antibiotic was started earliest on the 4-th day.

The second most important comment is related to the antibiotic dosage. In the last years most of the Gram negative germs have developed resistance[6] especially to II-nd and III-rd generation cephalosporines, by ESBL (Extended Spectrum Beta-Lactamases). In order to overcome this phenomena we either used BL – inhibitors (clavulanic acid, sulbactams, tazobactams), or we increased the dosage. In the later case The Sanford Guide 2003 recommends increased doses by a two or three fold.

The third comment is about the delayed adequate treatment. There is a myth about "having time" to correct the antibiotic therapy, later, according to the antibiogram. The fact is that many studies (Fig. 1) showed that inadequate initial treatment could increase mortality, even if antimicrobial treatment is later corrected using antibiograms.[12] Even if the figures vary, the general idea is that the rate of complications is increased by 250%, and the mortality by 200%, if the initial antibiotic therapy is inadequate. So getting it right the first time is very important. In our cases beside the antibiotics surgical treatment was also performed in order to improve the outcome.

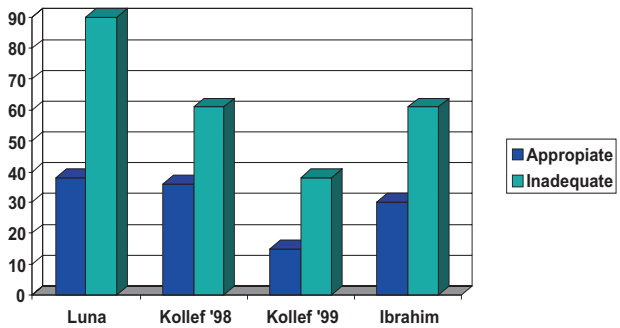

Figure 1. Mortality associated with initial inadequate therapy in critically ill patients with serious infections in the ICU [7-10]

Recent studies have documented that high costs are not only due to long hospital stay, but also due to a three fold increase of antibiotics, biochemistry, hematology, microbiology, radiology, and surgery costs.

Using an AB association (Tab. 4) as below might seem "inexpensive" but if we comply to the dosage recommended by Sanford Guide, and according to the reference price of antibitocs*, the daily costs of antibiotic treatment are the following:

· Cephalosporines+Aminoglicozides+Imidazoles		
- Cefobid +Gentamicin+Metronidazol =	1 593 000 *	= 46 USD
- Cefobid + Gentamicin+Metronidazol =	2 190 200 *	= 64 USD
- Ceftriaxon + Genta + Metronidazol =	578 000 - 1 024 000*	= 31 USD
- Ceftriaxon + Netilmicin + Metronidazol =	1 718 822*	= 54 USD
- Rocephin + Genta + Metronidazol =	2 520 606*	= 74 USD
- Cefoperazona + Netilmicin + Metronidazol =	3 230 000*	=95 USD
· Penicilins + BL-inhibitors + Aminoglicozides+Imidazoles		
- Piperacilin + Tazobactam + Netilmicin =	3 387 030*	= 100 USD
- Tazocin + Genta + Metronidazol =	2 689 036*	= 79 USD
- Augmentin + Genta + Metronidazol =	1 498 718 - 1 874 118*	= 58 USD
- Augmentin + Netilmicin + Metronidazol =	1 985 218 - 2 460 618*	= 72 USD
· Carbapanems		
- Ertapenem 1 x 1g/day =	1 790 000*	= 52 USD
- Imipenem-Cilastatin (4 X 0.5g) =	3 022 028*	= 88 USD
- Meropenem (3 X 1g) =	4 650 000*	= 134 USD

(* source: www.msf-dgf.ro)

De-escalation therapy™. Recent studies strongly suggest that the appropriate treatment should use de-escalation therapy meaning that is used from the begining of treatment the best possible empiric therapy. If later, no pathogen or less resistant pathogen is identified, the therapy can be discontinued or de-escalated to one with a narrower coverage.[13,14] Thus, one is fully covered from the start, during the early stages of treatment. De-escalation therapy allows physicians to administer first the broadest antibiotic spectrum in critically ill patients in order to prevent rapid decline, avoid resistance, and save lives.

All carbapenems offer an excellent coverage. The latest of the carbapenems, Ertapenem DCI, is dedicated to communitary infections, due to it's spectrum, being active on all germs involved; the plasmatic concentration / 24 hours does not drop under 2 mg/ml, and the MIC are E Coli = 0,016 mg/ml, Bacteroides=0,500 mg/ml, Proteus=0,125 mg/ml, Clostridium = 0,050 mg/ml, Peptostreptococus=1 mg/ml, Streptococus P=1 mg/ml, Klebsiella Sp=0,060 mg/ml, MSSA = 0,250 mg/ml. Ertapenem DCI can be an excellent choice for de-escalation.

The de-escalation therapy was originally designed for VAP, but later studies showed excellent results in all cases of severe sepsis or septic shock.[13,14] Further more, Namias et al.[13] showed that using carbapenems as initial empiric therapy does "not lead to the emergence of resistant bacteria". Using carbapenems is not as expensive as it might seem (see above), and if considered in the context of ICU costs, those costs are of lesser importance.

We used de-escalation therapy in one case (case 7), on a patient with septic shock, with good results, both as general status and rapid local improvement.

AB therapy was continued for 14-21 days, depending on general status and individual evolution[14]. Once the surgical wound was clean and granulation was present, antibiotics were discontinued.

Parenteral/enteral feeding

The first 24-36 hours are dedicated to volemic replacement, and MOSF correction. After this, minimal parenteral feeding, using glucose 10% and aminoacids, is useful. Oral feeding should be resumed as soon as possible. Prolonged tracheal intubation and assisted ventilation should not affect gastric tube feeding. Physiological advantages and cost/efficiency ratio favor enteral feeding. [15,16]

Preoperative preparation includes naso-gastric aspiration, monitoring of urine output, SaO2, and oxygen therapy, if necessary.

Surgical treatment.

Until the 90's there was a misconception of "conservative" surgery, meaning the incisions would be a way to drain the infection, and excisions would be limited, in order to preserve as much tissue as possible, especially the skin, in order to achieve an early healing and avoid skin grafts. Second of all, there was "the operation" followed by several dressing changes, which literally ment only dressing changing, with no or very little debridment. This resulted in poor recovery with high mortality (an early study revised 4 cases of severe soft tissue infections of the perineum, between 1987 and 1990, with a survival rate of only 25%).

Today main objective, is to remove as correct as possible (neither extensive, nor excessive) the dead tissues, tissues without a good capillary circulation. Those tissues are basically a bacteria culture medium.

First of all, timing is essential. Volemic replenishment is crucial, in the first stage more important than antibiotherapy, or any other therapeutic measure.

It is obvious that the first operation is of most importance, as is the first excision of the affected tissues. As a general rule, all suspect/poor looking soft tissue must be surgically removed. This is followed by an energetic mechanic lavage of the wound, using warm saline solutions (NaCl 0.9%). The toilet of the wound is mechanical not chemical; usage of different antiseptics should be discouraged, especially peroxides (H_2O_2 which is caustic and will induce more tissue damage) and iodine. Antibiotics are at least useless, if not dangerous, on topical application. The dressing must be humid, using saline (NaCl 0.9%) or betaisodona 1-2 % (the betaisodona / polividon-iodine solution of 10% is diluted 1/5-1/10 in saline).

"Programmed surgery" is the key of successful treatment. Every day the patient is brought into the OR and under short general anesthesia, the wound is revised. All dead tissues are removed; the secretions are washed off with saline solution. In one case (case report 1) the whole scrotum was "lost", and after 6 months the patient displayed a "magical " recovery: the testis, was in a "neo" scrotum. Fascias are the biggest problem: since they do not have capillaries, they have the lowest healing rate. Abdominal fascia excision might pose some difficult problems, since they have a major resistance role. In one case (case report 5) the external oblique muscle fascia was completely excised, on the right side, and replaced with a mesh fastened with transfixiant separate sutures, in order to prevent evisceration, due to postoperative increased intraabdominal pressure. The mesh was later removed, when the wound was covered with granulation tissue, and the skin defect was covered by "dynamic skin suture technique". In case report 6 the whole abdominal defect was replaced by a "Certex" synthetic mesh (umbilical hernia). The mesh granulated and then was grafted, with surprisingly good results (since there was no other option, the skin defect being much larger then the mesh).

General anesthesia is essential for minimizing the patient's suffering and for a correct local treatment, meaning excisions and aggressive scrubbing with saline solution (NaCl 0.9%).

In all cases (case reports 5, 6) where the wound was in the abdominal area, we wrapped the abdomen with a sterile sheet, fastened by sawing. This allowed the patient to move freely in the bed, and also allowed proper nursing, without the risk of dressings to fall of, or abdominal evisceration.

Definitive healing was "per secundam" as in some cases of perineal gangrene (case report 1), or by free grafting, rotated flaps, "Italian" flaps, or more recent by "dynamic skin closure ".

CONCLUSIONS

1. Extensive soft tissue infections are a serious health problem and can generate high mortality, ranging from 15% to 40%.

2. Treatment is a local and systemic fierce battle.

3.Surgical treatment should be aggressive and tireless, with daily revisions of the wound, in general anesthesia, as long as it is necessary.

4.The treatment is expensive, due to long hospitalization, long admissions in ICU with high costs, daily programmed operations, and high consumption of drugs, antibiotics and sterile dressings.

5.Daily programmed operations, require sustained efforts from the surgical team (surgeons, doctor's assistants, nurses, stretcher-bearers) and from the anesthesia team (doctors and nurses), disregarding holidays and weekends.

6.Good results are based on personal dedication of all medical staff involved in the treatment process: doctors, doctor's assistants, nurses, stretcher-bearers, and housekeepers.

REFERENCES

1. American College of Chest Physicians, Society of Critical Care Medicine. Consensus Conference: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med 1992;6:864-74.
2. Paun C, Flangea C. Asipratele bronsice. Sensibilitatea la antibiotice. Importanta antibioterapiei conform antibiogramei. Terapeutica Farmacologica si Toxicologie Clinica volVI;3:75.
3. Fluit AC, Schmitz FJ, Verhoef J. Frequency of isolation of pathogens from bloodstream, in nosocomial pneumonia, skin and soft tissue, and urinary tract infections occurring in european patients. Eur J Clin Microbiol Infect Dis 2001;20(3):188-91.
4. Choi PT-L, Yip G, Quinonez LG, et al. Crystalloids vs. colloids in fluid resuscitation; a systematic review. Crit Care Med;1999;27:200-10.
5. Ruef C. Significance of antibiotic resistance in treatment of soft tissue infections. Ther Umsch 2002;59(1):41-5.
6. Drusano GL. Prevention of Resistance. Clin Inf Dis 2003;36.
7. Luna CM, Vujacich P, Niederman MS. Impact of BAL data on the therapy and outcome of VAP. Chest 1997;111:676-85.
8. Ibrahim EH, et al. Modification of empiric treatment in patients with VAP. Chest 2000;118L:146-55.
9. Kollef MH, Sherman G, Ward S. Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. Chest 1999;115:462-74.

10. Kollef MH, Ward S. The influence of mini-BAL cultures on patient outcomes: implications for antibiotic management of VAP. Chest 1998;113:412-20.
11. Simon D, Trenholme G. Antibiotic selection for patients with septic shock. Crit Care Clin 2000;16(2):215-31.
12. Kolef MH, Sherman G, Ward S, et al. Inadequate antimicrobial treatment of infections: A risk factor for hospital mortality among critically ill patients. Chest 1999;115;462-74.
13. Namias N, Harvill MD, Sarah RN, et al. Empiric treatment of sepsis in the surgical intensive care unit with broad spectrum antibiotics for 72 hours does not lead to the emergence of resistant bacteria. J of Trauma, Infection and Critical Care 1998;4505:887-91.
14. Dorobat C, Dorobat Gh, Teodor A, et al. Terapia de prima intentie cu Tienam (Imipenem, DCI). Studiu cost-eficienta. Terapeutica Farmacologica si Toxicologie Clinica vol.VI;3:79.
15. Adant JP, Bluth F, Fissette J. Necrotizing fascitis: a life-threatening infection. Acta Chirr Belg 1998;98(3):102-6.
16. Fry DE. Sepsis syndrome. Am Surg 2000;66(2):126-32.