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Attenuation of MODS-related and ARDS-related mortality makes infectious complications a remaining challenge in the severely injured

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ABSTRACT

Introduction The recent decrease in multiple organ dysfunction syndrome (MODS)-associated and adult respiratory distress syndrome (ARDS)-associated mortality could be considered a success of improvements in trauma care. However, the incidence of infections remains high in patients with polytrauma, with high morbidity and hospital resources usage. Infectious complications might be a residual effect of the decrease in MODS-related/ARDS-related mortality. This study investigated the current incidence of infectious complications in polytrauma.

Methods A 5.5-year prospective population-based cohort study included consecutive severely injured patients (age >15) admitted to a (Level-1) trauma center intensive care unit (ICU) who survived >48 hours. Demographics, physiologic and resuscitation parameters, multiple organ failure and ARDS scores, and infectious complications (pneumonia, fracture-related infection, meningitis, infections related to blood, wound, and urinary tract) were prospectively collected. Data are presented as median (IQR), p<0.05 was considered significant.

Results 297 patients (216 (73%) men) were included with median age of 46 (27–60) years, median Injury Severity Score was 29 (22–35), 96% sustained blunt injuries. 44 patients (15%) died. One patient (2%) died of MODS and 1 died of ARDS. 134 patients (45%) developed 201 infectious complications. Pneumonia was the most common complication (50%). There was no difference in physiologic parameters on arrival in emergency department and ICU between patients with and without infectious complications. Patients who later developed infections underwent more often a laparotomy (32% vs 18%, p=0.009), had more often pelvic fractures (38% vs 25%, p=0.02), and received more blood products <8 hours. They had more often MODS (25% vs 13%, p=0.005), stayed longer on the ventilator (10 (5–15) vs 5 (2–8) days, p<0.001), longer in ICU (11 (6–17) vs 6 (3–10) days, p<0.001), and in hospital (30 (20–44) vs 16 (10–24) days, p<0.001). There was however no difference in mortality (12% vs 17%, p=0.41) between both groups.

Conclusion 45% of patients developed infectious complications. These patients had similar mortality rates, but used more hospital resources. With low MODS-related and ARDS-related mortality, infections might be a residual effect, and are one of the remaining challenges in the treatment of patients with polytrauma.

Level of evidence Level 3.

Study type Population-based cohort study.

INTRODUCTION

Advances in pre-hospital and in-hospital trauma care have attributed to a decrease in mortality in trauma in the past decades.[1–3] Although improvement in hemorrhage control and resuscitation has been established, patients can still deteriorate at a later stage due to inflammatory (eg, infectious) complications. After injury, the innate immune system is activated resulting in an inflammatory response with a key role for neutrophils. Sometimes, however, these processes of inflammatory response become dysregulated, and immune-mediated complications may occur such as multiple organ dysfunction syndrome (MODS) and adult respiratory distress syndrome (ARDS).[4]

Several studies including our own have observed that MODS-related and ARDS-related deaths have decreased over the last years resulting in more severely injured patients surviving.[5 6] However, we also observed that many surviving patients developed infectious complications. Since infectious complications are also an expression of the failure of the immune system of the host, we hypothesized that a decrease in death by MODS and ARDS has resulted in a residual problem of (less deleterious) infectious complications. Therefore, we conducted a prospective population-based cohort study in patients with polytrauma to investigate the current incidence of infectious complications.

MATERIALS AND METHODS
Study setting

The study was conducted at an urban major (Level-1) trauma center. From November 2013, a 5.5-year prospective population-based cohort study was undertaken to investigate outcomes in severely injured patients admitted to the intensive care unit (ICU) of the University Medical Center Utrecht, the Netherlands. Detailed characteristics of the hospital and catchment area were previously described.[7] All consecutive severely injured patients >15 years of age who were admitted to ICU either directly from the emergency department (ED) or postoperatively after urgent surgery and survived >48 hours were included. Patients with isolated injury to the brain (Abbreviated Injury Score (AIS) head three or more and AIS two or less in other regions), asphyxiation, drowning and burns were excluded, because of possible different physiologic response to severe trauma and a significantly different mortality and morbidity profile.[8 9] A flowchart of patient inclusion is shown in figure 1.
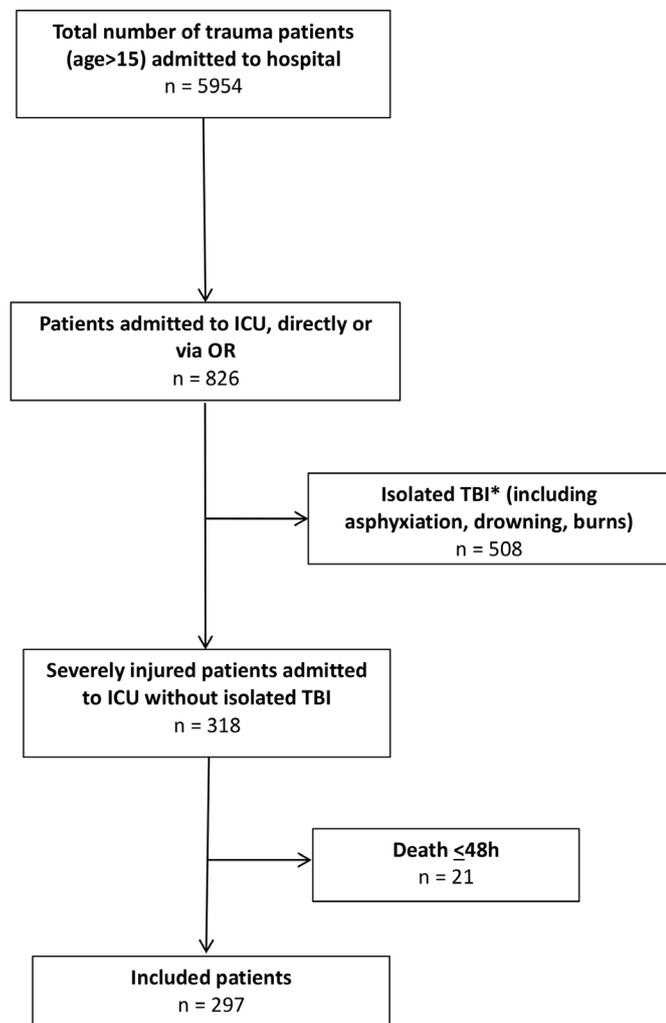
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Figure 1 Flow diagram of included patients. *Isolated traumatic brain injury (TBI) was defined as Abbreviated Injury Score (AIS) head >3 and AIS<2 or less in other regions. ICU, intensive care unit.

Data collection

All data were prospectively collected on arrival in ED and on a daily basis in ICU by the authors (KW and LL) and included patient demographics, Injury Severity Score (ISS), shock and resuscitation parameters. Admission arterial blood gas analysis, coagulation status, and temperature measurement were performed during resuscitation in ED as part of standard procedures. Arterial blood gas analysis and temperature measurement were repeated on arrival in ICU. Urinary output was measured the first hour after arrival in ICU. Blood product (packed red blood cells (PRBC), fresh frozen plasma (FFP) and platelets (PLT)) use was recorded in the first 24 hours following admission. Infectious complications were registered by the treating physicians (surgeons and/or intensivists) and categorized as pneumonia, fracture-related infections, positive blood culture, septic shock, abdominal abscess, wound infection, thrombophlebitis, thorax empyema, urinary tract infection (UTI), secondary meningitis after traumatic brain injury, and miscellaneous complications (including, cholecystitis, otitis, pancreatitis, and pericarditis). Furthermore, both Denver multiple organ failure (MOF) scores[10] and ARDS Berlin criteria[11] were registered daily up until 28 days or discharge from ICU. Denver MOF score was chosen over other MOF scoring systems like Marshall MODS or sequential organ failure assessment (SOFA) to avoid difficulties

by including the Glasgow Coma Scale (GCS) in the organ failure score. GCS can be challenging to obtain in patients with trauma in ICU because they are often sedated and intubated for extended periods. This could negatively influence the CNS organ failure score.[9 12 13]

Selective decontamination of the digestive tract (oropharynx and intestinal tract; SDD) was used in all patients admitted to ICU during the first 4 days and included administration of topical antibiotics in the gastrointestinal tract and systemic prophylaxis with an intravenous third-generation cephalosporin.[14]

Primary outcome was the incidence of infectious complications during hospital stay. Secondary outcomes were mortality, ARDS and MODS, ventilator days, ICU length of stay (ICU-LOS), and in-hospital length of stay (H-LOS).

Definitions

Urgent laparotomy was defined as a laparotomy that was performed in patients who were transported from ED directly (or via CT scan) to the operating room.

Different types of infections were defined according to the adapted the definitions from the Center for Disease Control and Prevention criteria,[15] American College of Surgeons Wound Schema,[16] Barts Health NHS Trust guidelines,[17] and consensus groups for specific types of infections.[18 19] Full definitions of specific infections were added as a supplemental table (online supplementary table S1).

Statistical analysis

Data were analyzed using IBM SPSS Statistics, V.25.0 (Armonk, NY, USA). Graphs were prepared with GraphPad Prism V.8.3.0 (San Diego, CA, USA). Results are presented as median and IQR. Comparison of variables was done using Kruksal–Wallis test or Pearson's χ^2 test in dichotomous data. Variables with univariate statistical significance of less than 0.10 were included in a multivariate logistic regression analysis. These variables were analyzed with forward stepwise selection to identify independent risk factors for infectious complications and presented as ORs and 95% CIs. Statistical significance was defined as p<0.05.

RESULTS

In total, 297 patients were included with a median age of 46 (27-60) years. Seventy-three per cent were men, 286 (96%) patients had blunt injuries, and median ISS was 29 (22-35) (table 1).

44 patients (15%) died; 33 due to brain injury (75%), 6 due to respiratory insufficiency (14%), 2 due to sepsis (5%), 1 due to bowel ischemia (2%), 1 died of MODS (2%), and 1 patient died of ARDS (2%). Median time to death for patients who did not die of brain injury was 15 (8–32) days.

134 patients (45%) developed 201 infectious complications. Pneumonia was the most common complication (49.8%), followed by fracture-related infection (12.4%). All other infectious complications occurred between 2% and 7% (table 2).

48 patients (36%) developed more than one infection during their hospital stay; 28 patients (21%) had two infections, 12 patients (9%) developed three infectious complications and 8 patients (6%) had more than three infectious complications.

Median time to infection development was 12 (7–20) days (figure 2A). Development of pneumonia, positive blood culture, and secondary meningitis after brain injury occurred roughly within the first week after injury, whereas septic shock, wound infection, and thrombophlebitis developed in the second week after injury. Fracture-related infection and thorax empyema

Table 1 Patient demographics, resuscitation, and outcome parameters

Demographics	Total cohort (n=297)	No infectious complications (n=163)	Infectious complications (n=134)	P value
Age (years)	46 (27–60)	44 (24–59)	50 (30–61)	0.08
Gender (% male)	216 (73)	111 (68)	105 (78)	0.05
MOI (%blunt)	286 (96)	154 (94)	132 (99)	0.12
ISS	29 (22–35)	29 (22–34)	29 (22–36)	0.48
AIS head	3 (1–4)	3 (1–4)	3 (1–4)	0.72
AIS face	0 (0–2)	0 (0–2)	0 (0–1)	0.15
AIS chest	3 (2–4)	3 (2–4)	3 (2–4)	0.12
AIS abdomen	2 (0–3)	2 (0–2)	2 (0–3)	0.75
AIS extr /pelvis	2 (1–3)	2 (1–3)	2 (0–3)	0.11
AIS external	0 (0–1)	0 (0–1)	0 (0–1)	0.30
Pelvic fracture	93 (31)	42 (25)	51 (38)	0.02*
Urgent laparotomy	71 (24)	29 (18)	42 (31)	0.009*
ED parameters				
SBP (mm Hg)	120 (100–136)	121 (100–142)	117 (96–132)	0.08
DBP (mm Hg)	75 (60–86)	78 (60–90)	74 (60–83)	0.05
Temperature (ºC)	35.5 (34.4–36.5)	35.4 (34.3–36.5)	35.5 (34.4–36.5)	0.78
Hb (mmol/L)	8.0 (7.2–8.9)	8.0 (7.4–9.1)	8.0 (7.2–8.9)	0.48
Leukocytes (x10^9/L)	15.3 (11.1–20.1)	15.3 (11.6–19.9)	15.3 (9.8–20.6)	0.56
Platelets(x10^9/L)	235 (190–281)	233 (190–288)	235 (187–277)	0.67
PT	15.2 (13.9–17.3)	15.1 (14.0–17.0)	15.5 (13.9–17.9)	0.34
pH	7.31 (7.26–7.37)	7.32 (7.26–7.38)	7.30 (7.25–7.35)	0.15
$PaCO_2$ (mm Hg)	46 (41–54)	46 (40–52)	47 (42–54)	0.19
PaO_2 (mm Hg)	202 (105–302)	221 (100–329)	198 (106–277)	0.35
BD (mmol/L)	3.0 (0.0–6.0)	2.5 (0.0–6.0)	3.0 (0.0–6.0)	0.63
Sat (%)	100 (97–100)	100 (97–100)	100 (98–100)	0.98
ICU Parameters				
SBP (mm Hg)	119 (105–136)	120 (106–136)	119 (105–137)	0.82
DBP (mm Hg)	65 (56–74)	66 (56–75)	65 (55–73)	0.38
Temperature (ºC)	35.3 (34.5–36.0)	35.4 (34.3–36.1)	35.3 (34.5–35.9)	0.70
Hb (mmol/L)	7.6 (6.8–8.3)	7.6 (6.8–8.3)	7.5 (6.8–8.2)	0.71
pH	7.33 (7.29–7.38)	7.34 (7.30–7.38)	7.33 (7.28–7.38)	0.68
$PaCO_2$ (mm Hg)	43 (38–47)	43 (39–47)	43 (38–47)	0.73
PaO_2 (mm Hg)	150 (114–192)	153 (116–190)	144 (108–198)	0.36
BD (mmol/L)	3.5 (1.5–5.7)	3.2 (1.4–5.5)	4.0 (1.5–6.1)	0.23
Sat (%)	98 (98–99)	98 (98–99)	98 (97–99)	0.10
UO (ml)	150 (80–300)	150 (80–310)	145 (71–295)	0.54
Resuscitation				
Crystalloids (L)				
<8 hours	4.7 (2.4–6.3)	4.5 (2.3–6.3)	4.8 (2.7–6.3)	0.31
<24 hours	7.4 (5.1–10.4)	7.3 (4.6–10.3)	7.9 (5.5–10.4)	0.19
PRBC (u)				
<8 hours	1 (0–4)	0 (0–3)	2 (0–6)	0.03*
<24 hours	1 (0–5)	1 (0–4)	2 (0–7)	0.06
FFP (u)				
<8 hours	0 (0–4)	0 (0–3)	1 (0–5)	0.04*
<24 hours	0 (0–5)	0 (0–4)	2 (0–7)	0.06
PLT (u)†				
<8 hours	0 (0–1)	0 (0–0)	0 (0–1)	0.04*
<24 hours	0 (0–1)	0 (0–1)	0 (0–1)	0.03*
Outcome				
Ventilator days	7 (3–11)	5 (2–8)	10 (5–15)	<0.001*

Continued

Table 1 Continued

Demographics	Total cohort (n=297)	No infectious complications (n=163)	Infectious complications (n=134)	P value
ICU-LOS (days)	8 (4–14)	6 (3–10)	11 (6–17)	<0.001*
H-LOS (days)	21 (13–33)	16 (10–24)	30 (20–44)	<0.001*
MODS	56 (19)	21 (13)	35 (25)	0.005*
ARDS	15 (5)	5 (3)	10 (7)	0.11
Mortality	44 (15)	27 (17)	17 (12)	0.41

Data are expressed as median (IQR) or absolute numbers (%).
*Statistically significant.
†1 unit of platelets contains five donors.
AIS, Abbreviated Injury Scale; ARDS, acute respiratory dysfunction syndrome; BD, base deficit; DBP, diastolic blood pressure; FFP, fresh frozen plasma; Hb, hemoglobin; H-LOS, hospital length of stay; ICU, intensive care unit; ISS, Injury Severity Score; LOS, length of stay; MODS, multiple organ dysfunction syndrome; MOI, mechanism of injury; PaCO2, partial pressures of carbon dioxide; PaO2, partial pressures of oxygen; PLT, platelets; PRBC, packed red blood cells; PT, prothrombin time; Sat, saturation; SBP, systolic blood pressure; UO, urinary output first hour in ICU.

developed around day 18, and abdominal abscess, UTI and all miscellaneous infectious complications developed approximately 25 days after injury (figure 2B).

Sixteen out of 44 patients (36%), who later died, developed an infectious complication, nine of them died while having an infectious complication. Three of them died because of the infectious complication, (two sepsis and one respiratory insufficiency after Staphylococcus aureus pneumonia); 1.0% of the whole studied population died of an infection.

Comparison of patients with and without development of infectious complications

Patients who later developed infectious complications had similar injury severity (ISS for both groups 29, p=0.48) and physiologic parameters on arrival in ED and ICU compared with patients without infectious complications (table 1). However, they underwent more often an urgent laparotomy (31% vs 18%, p=0.009), had more often pelvic fractures (38% vs 25%, p=0.02), received more PRBC, FFP, and PLT<8 hours, and more FFP and PLT <24 hours (table 1). They developed more often MODS (25% vs 13%, p=0.005), but there was no difference in ARDS development (7% vs 3%, p=0.11). Furthermore, they stayed longer on the ventilator (10 (5–15) vs 5 (2–8) days, p<0.001), longer in ICU (11 (6–17) vs 6 (3–10) days, p<0.001), and in hospital (30 (20–44) vs 16 (10–24) days, p<0.001). Nevertheless, there was no difference in mortality (12% vs 17%, p=0.41) between

Table 2 Incidence of different types of infections

Type of infection	N (%)
Pneumonia	100 (49.8)
Fracture-related Infection	25 (12.4)
Positive blood culture	14 (7.0)
Septic shock	13 (6.5)
Abdominal abscess	4 (2.0)
Wound infection	9 (4.5)
Thrombo-phlebitis	7 (3.5)
Thorax empyema	4 (2.0)
Urinary tract infection	7 (3.5)
Secondary meningitis	7 (3.5)
Miscellaneous*	11 (5.5)
Total†	201 (100)

*Including cholecystitis, otitis, pancreatitis, and pericarditis.
†48 patients developed more than one complication.

patients who later developed infectious complications and patients who did not (table 1).

Multivariate analysis (included parameters were age, male gender, urgent laparotomy, pelvic fracture, crystalloids and blood product administration both <8 and <24 hours, MODS) showed that age, urgent laparotomy and MODS were independent predictors for development of infectious complications (table 3) Table 3 Intraoperative abdominal organ injury related to infectious complications should be table 4 and table 4 Multivariate analysis: infectious complications in patients with polytrauma should be table 3

Urgent laparotomy related to development of infectious complications

71 patients (24%) underwent an urgent laparotomy, of whom four had no intra-abdominal injuries, but had pelvic packing for a pelvic
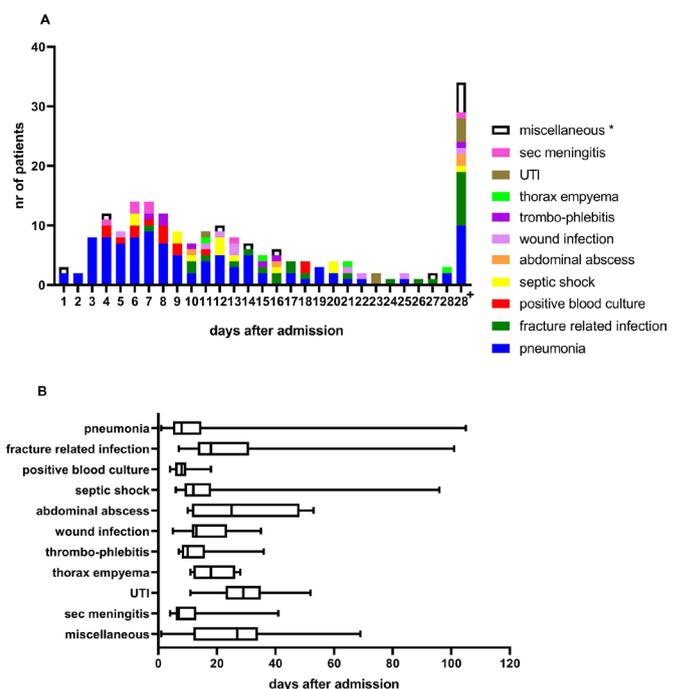

Figure 2 (A) Type of infectious complications related to days after admission. (B) Occurrence of different types of infectious complications over time. UTI, urinary tract infection, Sec meningitis, secondary meningitis after traumatic brain injury. *Miscellaneous infectious complications included cholecystitis, pancreatitis, pericarditis, and otitis.

Table 3 Intraoperative abdominal organ injury related to infectious complications

Type of injury*	Total (n=97)	No infectious complications (n=41)	Infectious complications (n=56)
No injury†	4	1	3
Solid organ injury	46	20	26
Hollow viscus injury	28	11	17
Large abdominal vessels	5	3	2
Abdominal wall/diaphragm	14	7	7

P=N.S.
*71 patients had 97 intra-abdominal injuries.
†All four patients without intra-abdominal injuries had pelvic packing for a pelvic fracture associated retroperitoneal hematoma.

fracture-related retroperitoneal hematoma. There was no difference in type of abdominal injury and the development of infectious complications (table 4). The infectious complications were not directly related to the laparotomy itself. In patients who had a laparotomy pneumonia and fracture-related infections were also the most common infectious complications.

DISCUSSION

Almost half of severely injured patients admitted to ICU who survived the first 48 hours, developed at least one infectious complication during hospital stay. Although there was no difference in ISS and physiological parameters, patients who later developed infectious complications had more often MODS, needed more blood products, and used more hospital resources (more ventilator days, longer stay in ICU and in hospital). There was however no difference in mortality between patients who later developed infectious complications and patients who did not. One per cent of the studied population died of an infectious complication.

Pneumonia was the most common infection followed by fracture-related infection. Median time to infection development was 12 days, although different infections developed during different time periods after admission.

Literature is equivocal on the relation between mortality and infectious complications. Some authors report higher mortality

Table 4 Multivariate analysis: infectious complications in patients with polytrauma

Variable	β-coefficient	P value	OR	95% CI lower	upper
Step 1*					
MODS	0.847	0.007	2333	1264	4306
Constant	−0,317	0.020	0.729		
Step2†					
Urgent laparotomy	0.650	0.025	1916	1085	3386
MODS	0.817	0.010	2263	1219	4203
Constant	−0,466	0.002	0.627		
Step3†					
Age	0.013	0.048	1013	1000	1026
Urgent laparotomy	0.747	0.012	2111	1178	3782
MODS	0.716	0.026	2045	1089	3840
Constant	−1,060	0.002	0.346		

*Variable(s) entered on step 1: MODS.
†Variable(s) entered on step 2: urgent laparotomy.
‡Variable(s) entered on step 3: age.
MODS, multiple organ dysfunction syndrome.

rates in patients who developed infectious complications,[20][21] whereas others, including our own data, showed similar mortality rates.[17] This discrepancy might be partly explained by the different infectious complications that have been reported; sepsis is for example more lethal than pneumonia or surgical site infections.[21]

Previous studies have shown comparable results regarding percentage and type of infectious complications; roughly half of severely injured patients developed infectious complications and the most common infectious complication was of respiratory origin.[17][20] Different infections developed at different times during admission; Cole et al showed the same singularity in their study with early development of respiratory infections, and positive blood cultures, and later development of other infections.[17] Results were however not entirely comparable, since different types of infections were registered in both studies. Several studies have shown that the neutrophil response is dependent on which bacterial species the cell is attempting to kill. It is likely that different types of infections are caused by different bacteria, and that some bacteria are better resistant to neutrophils than others, resulting in different times of development of infections.[22][23] Possibly, exhaustion of the innate immune system with decreased response of neutrophils plays an important role in the selection of bacteria causing different infectious complications during different times after injury.

In our study age, the need for urgent laparotomy and MODS were independent predictors for development of infectious complications in patients with polytrauma. Other studies reported other independent predictors such as admission shock parameters,[17] gender, blood transfusions, AIS chest, and GCS on scene.[20] In our study, there was no difference in admission shock parameters between patients who later developed infections and patients who did not, although we did demonstrate that blood transfusion was associated with infectious complications. This association has been reported by others as well.[17][20][24][25] The fact that admission shock parameters in our study were not associated with infections could be possibly explained by the fact that in our cohort parameters such as blood pressure and hemoglobin were within normal ranges on arrival in ED. This phenomenon in which severely injured patients in smaller service areas with short transport times do not have deranged physiologic parameters on arrival in the ED has been described earlier.[6][7] These patients do not have the time to deteriorate because they are in the hospital before blood pressure, BD, and hemoglobin will change distinctly. One could argue that these patients were not severely injured at all. This is contradicted by the fact that patients had an ISS of 29, 31% had a pelvic fracture, 24% needed an urgent laparotomy, and they were all admitted to the ICU since that was one of the inclusion criteria. The studied cohort included the sickest patients with trauma admitted to our major trauma center. It is likely that the need for urgent laparotomy in our study reflects shock parameters in other studies. Furthermore, it is known that laparotomy as a second hit has an effect on the immune response and is associated with development of infections.[20]

As we have previously shown, MODS-related and ARDS-related death in trauma has decreased over the years and our previous studies have shown MODS- and ARDS-related death of less than 5%.[5][6] Since both MODS/ARDS and infections are neutrophil-mediated complications, it is tempting to speculate that infectious complications are the residual (and less severe) effect of the diminishing more severe MODS and ARDS.

This theory seems to be in line with the timing of the complications. Nowadays, time to MODS development is early after injury (3 days after injury) as we have shown in previous studies,[6] whereas median time to development of infectious

complications was 12 (7–20) days in this study. This means that MODS precedes infectious complications. Since MODS-related mortality was very low in our cohort (2%), surviving patients may later develop infectious complications. This philosophy is confirmed by the fact that MODS was an independent predictor for infectious complications.

All patients admitted to ICU received SDD, selective oropharyngeal decontamination, and systemic prophylaxis with an intravenous third-generation cephalosporin. This policy was introduced to reduce the incidence of ICU-acquired respiratory tract infections.[26] One could dispute that this could have influenced the micro-bacterial growth. However, first of all, all included patients received this regimen of antibiotic prophylaxis, so there was no difference in patients who later developed infectious complications and those who did not. Second, it has been previously shown that there was no overall ecological effect of prolonged antibiotic prophylaxis by counting resistant microorganisms in ICU in countries where there is relatively low rates of resistant micro-organisms.[27]

One of the limitations of this study is that it was conducted at a single institution in which the clinical treatment and research were conducted by the same clinicians. Another limitation is that data on the type of bacteria that caused infections were not routinely collected. Furthermore, no pre-existing medical conditions were documented.

In conclusion, in this population of severely injured patients almost half of patients developed an infectious complication. With improvements of trauma and critical care death by complications such as MODS and ARDS has decreased. This success has likely resulted in a shift to less deleterious infectious complications. Future studies need to focus on the role of the immune system (eg, neutrophil function) on the development of infectious complications. Early recognition of development these complications might lead to possible prevention. This could also have a considerable beneficial impact on the use of hospital resources.

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