Immunoparalysis in Trauma: The Crush Syndrome & Infections by MDR organisms

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No Conflict of Interest regarding the presentation …

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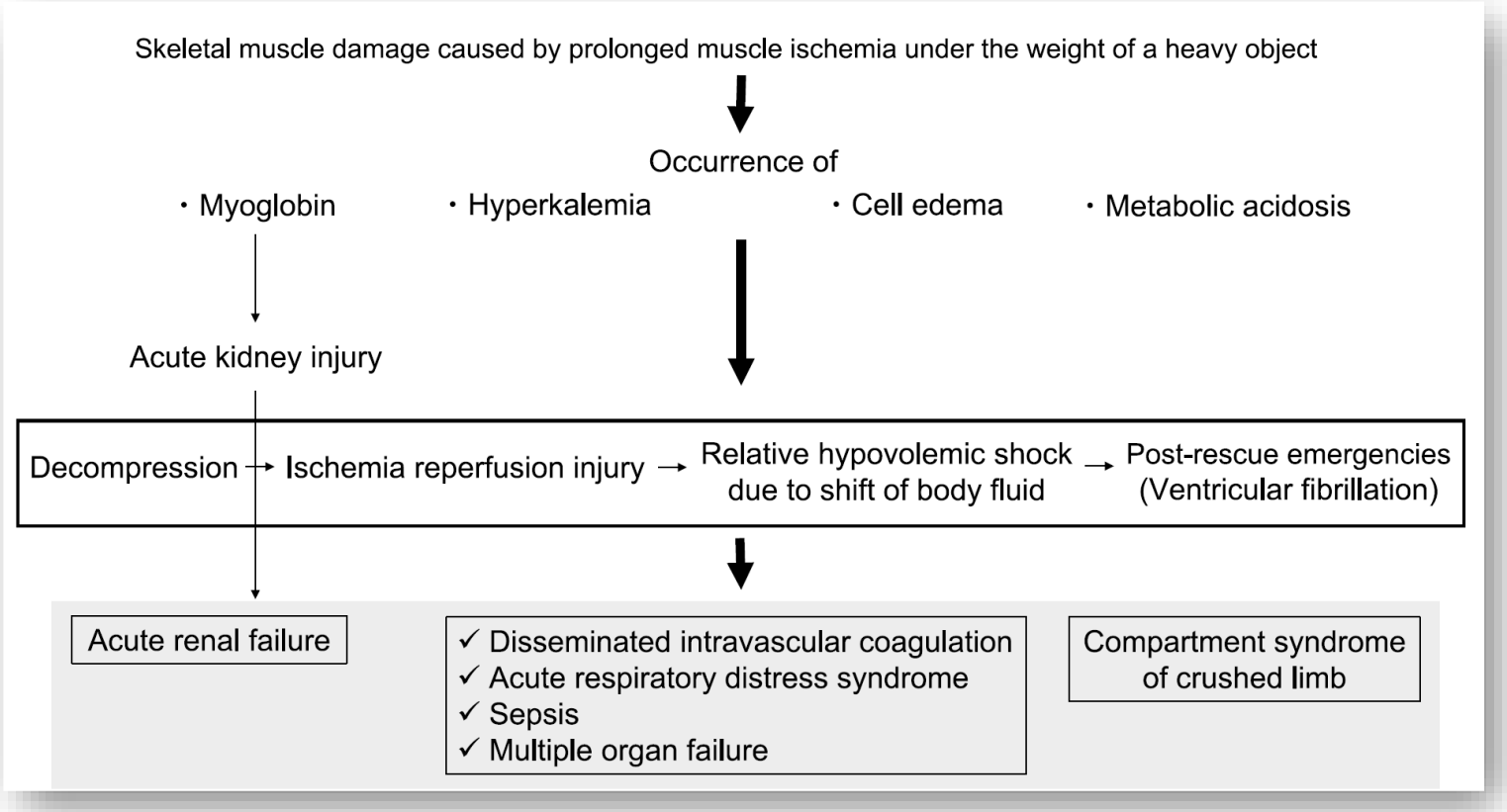
Crush injury	• Result of direct physical trauma to the torso, extremities, or other parts of the body from an external crushing force. • Leading to muscle necrosis, compartment syndrome, central and peripheral neurologic dysfunction, acute abdomen, thoracic trauma.
Crush syndrome	• Crush injury + systemic manifestations • Acute kidney injury and/or other organ failures and death

Crush syndrome: a review for prehospital providers and emergency clinicians

Usuda *et al. Journal of Translational Medicine* (2023) 21:584

- Incidence 2-15%, dialysis requirement up to 75%, mortality up to 48%
- 2nd most common cause of death after direct trauma after earthquakes
- Rhabdomyolysis due to compression and decompression (ischemia reperfusion injury)



Causes

Traumatic	Non-traumatic
• Accidents • Disasters (earthquakes …)	• Prolonged immobilisation • Metabolic, toxic, ischemic rhabdomyolysis

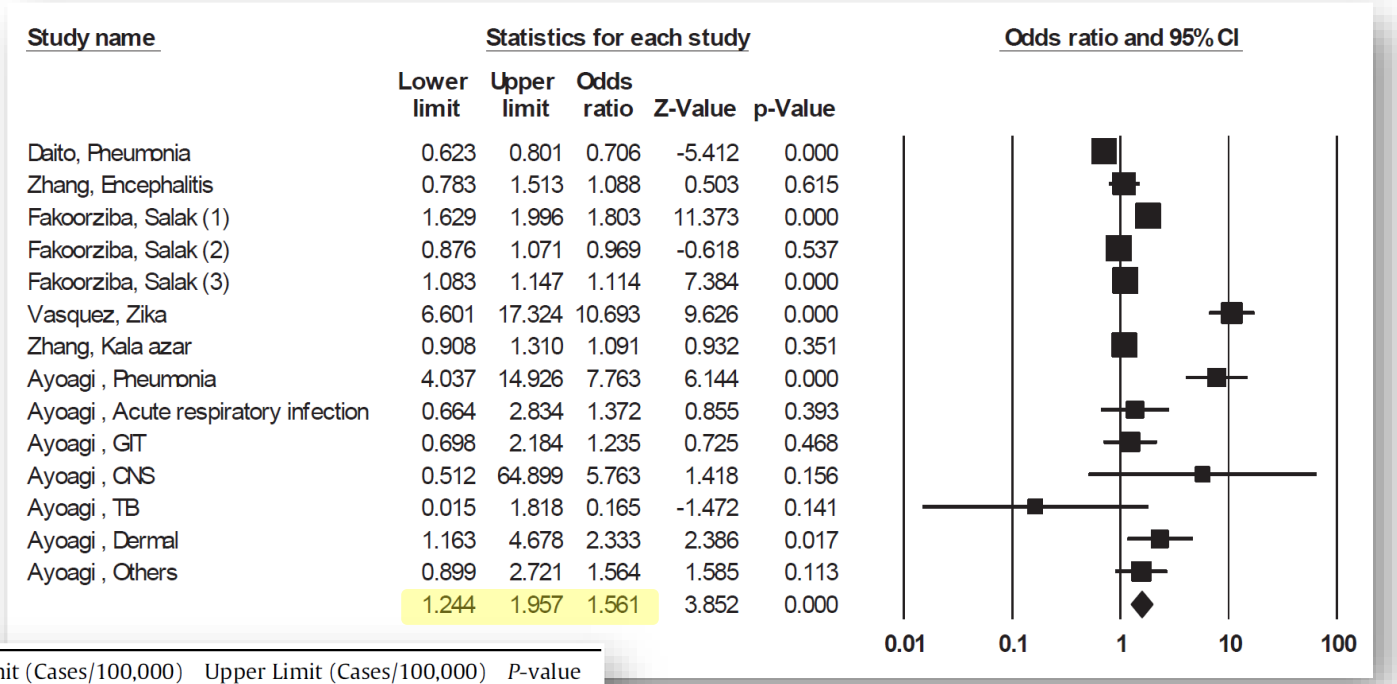
Management

- General trauma management
  - A, B, C …
  - Surgical interventions
    - Fasciotomy, amputation …
- Fluid, electrolyte (K, Ca, P …) and acid-base management
- Treatment of hyperkalemia and prevention of its complications
  - Calcium to prevent sudden death due to hyperkalemia
  - Renal replacement therapy
- Treatment of organ failures
- Prevention of critical illness complications
  - **Infections**
  - Malnutrition
  - ICU-acquired weakness
  - …

Incidence of infectious diseases after earthquakes: a systematic review and meta-analysis

Public Health 202 (2022) 131–138

Sara Najafi [a, f], Arash Akahavan Rezayat [a, b, f], Seyyedeh Faezeh Beyzaei [a], Zahra Shahriari [a], Mahdieh Taheri tabar [a], Mohammad Ghasemi Nour [a], Reza Mosaed [c, d], Majid Khadem-Rezaiyan [e], Ramin Hamidi Farahani [b, *]



Disease Category	Subgroup	Number of Studies	Event Rate (Cases/100,000)	Lower Limit (Cases/100,000)	Upper Limit (Cases/100,000)	*P*-value
Prevalent diseases						
Respiratory	Acute respiratory infection	3	328.5	133.3	807.2	0.000
	Tuberculosis	2	0.7	0.0	258.6	0.000
	Pneumonia	10	7.0	2.1	22.8	0.000
	Pertussis	3	0.7	0.2	3.1	0.000
	Valley fever	2	58.7	16.1	214.1	0.000
	Others	2	23.1	0.0	93476.2	0.137
	Total	22	9.9	3.5	27.7	0.000
GIT	Viral hepatitis	4	456.6	118.5	1743.4	<0.001
	Diarrhoea & GIT infections	4	56.8	5.6	572.3	0.000
	Total	8	163.4	31.0	858.1	0.000
CNS	Meningococcal meningitis	4	0.4	0.1	1.4	0.000
	Others	3	0.5	0.1	2.9	0.000
	Total	7	0.5	0.2	1.1	0.000
Dermal	Cutaneous leishmaniasis	6	471.7	142.8	1546.6	0.000
	Others	3	0.5	0.0	1.1	<0.001
	Total	9	84.5	27.1	262.8	0.000
Others	Malaria	8	6.2	0.3	131.0	<0.001
	German measles	2	1.4	0.0	53.0	0.000
	Typhoid fever	3	7.4	1.9	29.9	0.000
	HIV	2	1.6	0.0	4393.4	0.007
	Others	5	2.2	0.9	5.2	0.000
	Total	20	4.4	1.9	9.9	0.000

Hospital-acquired infections following the 1999 Marmara earthquake

Journal of Hospital Infection (2002) **51**: 47–51

O. Öncül*, Ö. Keskın†, H. V. Acar‡, Y. Küçükardalı§, R. Evrenkaya¶, E. M. Atasoyu¶, C. Top§, S. Nalbant§, S. Özkan‡, G. Emekdaş||, Ş. Çavuşlu*, M. H. Us**, A. Pahsa*, M. Gökben‡

- 630 trauma victims, 84% hospitalized, 19% HAI, 47% wound infection, 10% mortality (68% within 48 hrs)
- 15 (31%) Acinetobacter baumanii; 2 PDR
- 9 (19%) Staphylococcus aureus; all MRSA
- 7 (15%) Pseudomonas aeruginosa; 1 PDR
- 6 (13%) E coli
- 6 (13%) Klebsiella p.
- 2 (4%) S maltophilia

Table I *Data of 220 patients hospitalized > 48 h*

	HAI ($N = 41$)	Non-HAI ($N = 179$)
Age (years)	33.51 (17–90)	36.43 (2–67)
Mortality (%)	34.1	1.7
Time under rubble (h)	15.9*	13.8
Discharge	17.96† ($N = 27$)	15.25† ($N = 176$)
Death	26.86 ($N = 14$)	20.48 ($N = 3$)
Length of stay (day)	29.54*	18.86
Discharge	24.56† ($N = 27$)	16.39† ($N = 176$)
Death	14.83 ($N = 14$)	10.66 ($N = 3$)

The characteristics of infections in crush syndrome

R. Kazancioglu[1], A. Cagatay[2], S. Calangu[2], D. Korular[1], A. Turkmen[1], N. Aysuna[1], S. Sahin[1], S. Bozfakioglu[1] and M. S. Sever[1]

Clin Microbiol Infect 2002; 8: 202–206

- 40 patients, 22% died due to sepsis
- Average time under ruble 13 hrs
- 75% fasciotomy
- 95% culture positive
- 36% Acinetobacter spp.
- 21% Pseudomonas aeruginosa
- Majority resistant to Carbapenems but sensitive to quinolones

Table 1 The frequency of isolation of different bacterial species

	Wound culture	Blood culture	Urine culture	Catheter culture
Acinetobacter spp.	23	–	–	1
Pseudomonas aeruginosa	11	2	1	–
Methicillin-resistant *Staphylococcus aureus*	9	4	1	5
Serratia marcescens	2	–	–	–
Klebsiella pneumoniae	2	–	–	–
Enterobacter spp.	2	–	–	–
Candida albicans	2	–	–	–

Antimicrobial-Resistant Infections after Turkey/Syria Earthquakes, 2023

Emerging Infectious Diseases Vol. 29, No. 6, June 2023

Anthony Rizk, Antoine Abou Fayad, Louis-Patrick Haraoui

- Antimicrobial-resistant Acinetobacter baumannii has been identified in disproportionately high rates from infections associated with large-scale earthquakes

Table. Characteristics of earthquake-associated infections with antibiotic-resistant pathogens

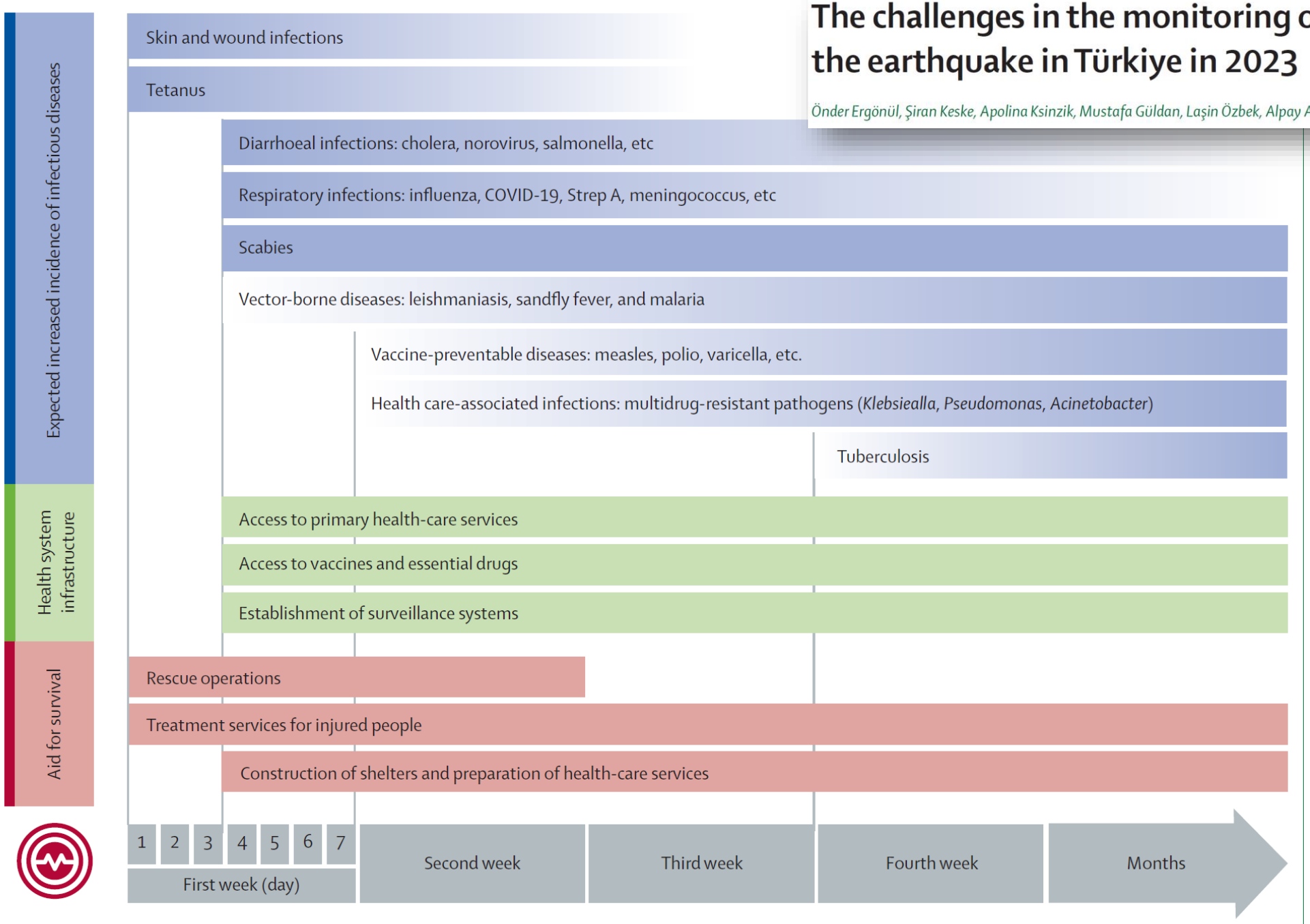
Earthquake location, date	Severity	Casualties	Key contaminants of earthquake-associated wounds
Marmara, Turkey, 1999	7.4 magnitude, affecting an area of 200 km × 40 km	17,480 deaths, 43,953 injured	*Acinetobacter* spp. and *Pseudomonas aeruginosa* resistant to carbapenems and sensitive to quinolones; methicillin-resistant *Staphylococcus aureus* (*1*)
Southeast Asia, 2004	9.1 magnitude, triggering a massive tsunami	310,000 deaths, millions destitute	MDR *Acinetobacter* spp.; ESBL *Escherichia coli*; methicillin-resistant *Staphylococcus aureus* (MRSA); and *Aeromonas hydrophilia*, *Pseudomonas* spp., and *Candida albicans* (*2*).
Northern Pakistan, 2005	7.6 magnitude, with 140 aftershocks	>82,000 deaths, 3.3 million injured	MDR *Pseudomonas* spp., *Enterobacter* spp., and *Acinetobacter* spp. only susceptible to amikacin (*3*).
Wenchuan, China, 2008	8.0 maginitude	>69,000 deaths, 45.5 million destitute	MDR *Acinetobacter baumannii*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* (*4*,*5*).
Central Italy, 2009	5.9 magnitude	308 deaths, >1,000 injured	Extensively drug-resistant *Acinetobacter baumannii* belonging to *A. baumannii* sequence type 2 with bla_{OXA-23} (*6*)
Haiti, 2010	7.0 magnitude	>100,000 deaths	Three *A. baumannii* isolates belonging to 2 distinct clones and were identified as ESBL producers and found to be $bla_{CTX-M-15}$-positive. They were resistant to penicillins, broad-spectrum cephalosporins and aztreonam but susceptible to carbapenems (*7*).

Early-stage detection and aggressive infection-control practices (e.g., active surveillance, contact isolation, sampling of healthcare workers and hospital environments, and antimicrobial stewardship) during and after disasters play key roles in preventing resistant strains from becoming endemic to healthcare facilities (*10*). Healthcare facilities may need to consider patient decolonization through chlorhexidine bathing to forestall colonization by antimicrobial-resistant *Acinetobacter* strains (*10*). Communities affected by the recent earthquakes will probably experience their effects for months to come. It is not too late to act to prevent further complications from these natural disasters, such as antimicrobial-resistant infections, from compounding ongoing human tragedies.

The challenges in the monitoring of infectious diseases after the earthquake in Türkiye in 2023

Lancet Infect Dis 2023; 23: e482–88

Önder Ergönül, Şiran Keske, Apolina Ksinzik, Mustafa Güldan, Laşin Özbek, Alpay Azap, Serap Şimşek-Yavuz, Füsun Can, Sibel Sakarya



- 2 large earthquakes on the 6th of February 2023 in Türkiye (hitting 11 provinces) and Syria
- More than 50,000 people passed away, over 100,000 people were injured, around half a million buildings were damaged

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	Situation in the region before the earthquakes	Comment
Gastrointestinal infections		
Cholera	An 2022 outbreak that started in Syria and resulted in >100 000 suspected cases, with 30% of infections in İdlib near the Turkish border[42]	The outbreak should be carefully monitored because of the poor sanitation conditions in Syria and Türkiye
Hepatitis A	Not reported in the earthquake-affected region of Türkiye, but 1354 cases reported among refugees in temporary shelters from 2012–2016[29]	Outbreak expected among unvaccinated population
Respiratory infections		
Measles	The vaccination rate was 90–92%,[11] and measles incidence between March, 2022, and February, 2023, was 5·46 per million,[24] which is the third highest rate in the WHO European region	Outbreak expected because of measles' high incidence in Türkiye[24] and interrupted vaccination services
Rubella	The incidence between March, 2022, and February, 2023, was reported to be the second highest in the WHO European region[24]	Outbreak expected because of rubella's high incidence in Türkiye[24] and interrupted vaccination services
Tuberculosis	Incidence of tuberculosis was reported as 18 cases per 100 000 people in Türkiye in 2021[29]	Because of overcrowding and disrupted health-care services, monitoring and control of tuberculosis is a challenge
Vector-borne infections		
Scabies	Reported[27]	Preventive treatment should be implemented
Malaria	Some provinces in the earthquake area are the old malaria region (southeastern provinces of Türkiye), and there are reported cases[29,30]	Emerging cases expected in the summer
Leishmaniasis	Cutaneous leishmaniasis was reported in the region[31]	Outbreak expected in warmer season
Sandfly fever	The vector (sandflies) is present and infections were reported[34]	Outbreak expected in warmer season
West Nile fever	West Nile fever seropositivity was detected in Mardin area in 52 (17%) of 307 tested individuals [32]	Outbreak expected in warmer season
Hospital-associated infections	Multidrug-resistant Gram-negative bacteria such as *Acinetobacter* spp and carbapenem-resistant *Klebsiella* spp are the leading challenges in the hospitals in Türkiye[35]	Stringent infection control measures should be implemented

The challenges in the monitoring of infectious diseases after the earthquake in Türkiye in 2023

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- Acute phase (1st wk)
  - Wound infections (25%)
  - Tetannus
  - Rabies
- Post-acute phase
  - Diarrhea, Hepatitis, Measles, Rubella, Scabies, Leishmaniasis, Tuberculosis …
- Late phase
  - Health-care associated infections

Among hospitalised earthquake victims, *Acinetobacter baumannii* and carbapenem-resistant *Klebsiella pneumoniae* were reported by infectious disease physicians to be the leading causes of hospital-acquired infections.[35]

Kahramanmaraş-Pazarcık Earthquake 2023: Characteristics of Patients Presented to the Emergency Department of a Tertiary Hospital Far from the Region and Infection Characteristics in Hospitalized Patients

Prehospital and Disaster Medicine 2024;39(1):25–31.

Özlem Çakın, Asist. Prof.;[1] Melike Yüce Aktepe, MD;[1] Samet Acar, MD;[2] Süleyman İbze, MD[3]

- 1294 adult patients admitted to ER
  - 117 ward admission
  - 20 ICU admission

	Culture Samples Studied within the First 48 Hours	Culture Samples Studied 48 Hours After Hospitalization
Urine Culture	Pseudomonas aeruginosa Enterocuccus faecıum (2) Escherichia coli	Candida albicans (3) Candida parapsilosis Candida tropicalis Escherichia coli (4) Enterocuccus faecıum (3) Klebsiella species (2) Acinetobacter baumannii Chryseobacterium indologenes Citrobacter freundii
Blood Culture	Proteus species MRSA	Klebsiella pneumoniae (3) CNS Candida glabrata
Catheter Culture		Klebsiella pneumoniae Stenotrophomonas maltophilia
Sputum Culture	Haemophilus influenzae Candida albicans	Pseudomonas aeruginosa Candida tropicalis
Tracheal Culture	Moraxella catarrhalis MRSA	Klebsiella pneumoniae (2) Acinetobacter baumannii Pseudomonas aeruginosa
Wound Pu Culture	Stenotrophomonas maltophilia Staphylococcus aureus Pseudomonas aeruginosa	Enterobacter cloacea Acinetobacter baumanii (2) Pseudomonas aeruginosa

Infections among adults hospitalized in intensive care after the 2023 earthquake in the southeastern part of Türkiye: a multi-center observational study

EK Kaya, B Halacli, G Guven, M Yildirim, AE Seven, E Gemcioglu, M Simsek, B Erdemir Sullu, RC Yuksel, ASKaynar, A Esmaoglu, B Kilicaslan, SB Akinci, K Gundogan, E Ortac Ersoy, J Rello, A Topeli. On behalf of the Turkish Intensive Care Studies-Network (TRICS-Net)

Unpublished, Under Evaluation

- Retrospective, multi-center, observational study conducted between February 6th and March 1st, 2023, in 6 ICUs of 3 tertiary referral hospitals that admitted earthquake victims

Variables	n=107
Age (yrs)	37 [27-57]
Female sex	58 (54.2)
Comorbidities	31 (28.9)
Diabetes mellitus	16
Hypertension	15
Hypothyroidism	7
Cardiovascular diseases	7
Respiratory diseases	3
Others	3
Time stuck under rubble (hrs)	12 [7-32]
Length of stay at the initial healthcare facility (hrs)	40 [17-76]
Admission reason	
Crush syndrome	70 (65.4)
Postoperative	27 (25.2)
Others	10 (9.4)
APACHE II Score	15 [12-20]
SOFA Score	3 [2-5]
GCS Score	15 [15-15]
Revised trauma score	12 [12-12]

Variables	n=107
Fasciotomy before admission	40 (37.4)
Amputation before admission	16 (15.0)
Acute kidney injury at admission	65 (60.7)
Intermittent hemodialysis before admission	29 (27.1)
Antibiotherapy before admission	15 (25.9)
Leukocyte count ($10^3/\mu L$)	13.7 [10.2-19.2]
CRP (mg/dl)	10.5 [6.1-16.7]
Procalcitonin (ng/ml)	1.78 [0.32-6.22]

	Positive culture within 72 hours 19%	Positive culture after 72 hours 32%
Source		
Wound	9	19
Lower respiratory tract	5	3
Urine	5	11
Central venous line	2	16
Blood	2	4
Microorganisms		
Acinetobacter baumannii	8	23
Klebsiella pneumoniae	4	12
Enterococcus spp.	4	7
MRSA	3	0
Escherichia coli	3	10
Enterobacter cloacae	3	1

- ✓8 *A baumannii* isolates are XDR (4 PDR)
- ✓4 *Klebsiella pneumonia* isolates; 1 MDR, 2 XDR, 1 PDR (3 carbapenem-resistant)
- ✓4 *Enterococcus spp.* isolates resistant to ampicillin but susceptible to vancomycin
- ✓3 *Escherichia coli* isolates; 2 MDR, 1 XDR
- ✓3 *Enterobacter cloacae* isolates; 2 MDR

TRICS-Net

	Amp	Amp-Sul	Vanco	Sulf-trim	CTX	Cefep	Ceftaz	Pip-Tazo	Amik	Genta	Cipro	Carbap	Colist
Wound													
A. baumannii 1		R		R					R	R	R	R	
A. baumannii 2	R	R		R			R	R	R	R	R	R	
A. baumannii 3	R	R		R		R	R	R	R	R	R	R	S
A. baumannii 4	R	R		R		R	R	R	R	R	R	R	
A. baumannii 5	R	R		R		R	R	R	R	R	R	R	
Enterococcus spp. 1	R		S										
Enterococcus spp. 2	R		S										
Enterococcus spp. 3	R		S										
Enterococcus spp. 4	R		S										
E. cloacae 1	R			S	R	S	R	R		S		R	
E. cloacae 2	R			S	S	S	S	S				S	
E. cloacae 3	R			S	R	S	R	S		S			
K. pneumonia	R			R	R	R	R	R	R	R	R	R	S
P. aureginosa							S	R	S		R	R	
MRSA	R		S										
Lower respiratory tract													
A. baumannii 1	R	R		R			R	R	R	R	R	R	S
A. baumannii 2	R	R		R			R	R	R	R	R	R	S
Urine													
K.pneumonia 1	R	R		R	R		R	R		S	R	S	
K.pneumonia 2	R			R	R	R	R	R	R	R	R	R	S
E. coli 1	R			S	R		R	S		S	R	S	
E. coli 2	R				R			S		S	R	S	
Blood obtained through the central venous line													
K.pneumonia	R	R		R	R	R	R	R	R	R	R	R	R
E. coli	R	R		R	R	R	R	R			R	R	
MRSA	R		S	S							R		
Blood													
A. baumannii	R	R		R				R	R	R	R	R	S
MRSA	R		S	S						S	R		

- Within 72 hours of ICU admission, antibiotics were administered to **92.5% of the patients with 79.8% receiving coverage for anaerobic infections**
- 51.5% exhibited positive culture results, and only **11.7% received appropriate antibiotic therapy**

	n=99
Ciprofloxacin+Clindamycin	22
Ceftriaxone+Metronidazole	18
Cefazolin+Metronidazole	14
Piperacillin-Tazobactam	9
Ampicillin-Sulbactam	9
Ceftriaxone	7
Ceftriaxone+Clindamycin	4
Ampicillin-Sulbactam+Metronidazole	3
Meropenem	3
Clindamycin	3
Cefazolin	3
Meropenem+Teicoplanin	1
Piperacillin-Tazobactam+Metronidazole	1
Cefazolin+Clindamycin	1
Ciprofloxacin	1

RECOMMENDATIONS FOR THE MANAGEMENT OF CRUSH VICTIMS IN MASS DISASTERS

NEPHROLOGY DIALYSIS TRANSPLANTATION
Mehmet Sukru Sever and Raymond Vanholder
Volume 27 Supplement 1 April 2012

Table 9. Suggested prophylactic/preemptive antibiotic treatment protocols in wound infections of traumatized victims [180–184]

Type of the trauma	Possible pathogens	Commonly accepted treatment[a]	Alternative
Head trauma	Staphylococci	Cefazolin	Ampicillin-sulbactam[b]
Maxillofacial fractures	Staphylococci	Cefazolin	Ampicillin-sulbactam
Chest thoracostomy	Staphylococci, streptococci	Cefazolin	Ampicillin-sulbactam
Abdominal injury	Gram-negative bacilli, anaerobes	Ceftriaxone + Metronidazole	Ampicillin-sulbactam
Bone fractures, closed	Staphylococci	Cefazolin	Ampicillin-sulbactam
Bone fractures, open	Staphylococci, Gram-negative bacilli	Cefazolin + Ciprofloxacin	Ampicillin-sulbactam
Fasciotomy	Staphylococci, Gram-negative bacilli, anaerobes	Cefazolin + Ciprofloxacin	Ampicillin-sulbactam
Crush with AKI	Staphylococci, Gram-negative bacilli, anaerobes	Cefazolin	Ampicillin-sulbactam
Burns	*Staphylococcus aureus, Pseudomonas aeruginosa, Acinetobacter* spp., fungi	Topical antimicrobials	

The European Renal Best Practice (ERBP) and the Renal Disaster Relief Task Force (RDRTF) of the International Society of Nephrology (ISN) recommend **preemptively using cefazolin and ciprofloxacin antibiotherapy** in patients with fasciotomy and/or open fractures

51% of patients who were admitted to ICUs after the earthquake had positive culture results (19% within 72 hours of ICU admission).

The most frequently identified microorganisms within 72 hours of ICU admission were *Acinetobacter baumannii*, *Klebsiella pneumonia*, *Enterococcus spp*, *Escherichia coli*, and *Enterobacter cloacae*.

Nearly all except for one *Enterobacter cloacae* isolate, exhibited MDR pattern.

Only 11.7% of patients received appropriate antibiotic therapy within 72 hours of ICU admission.

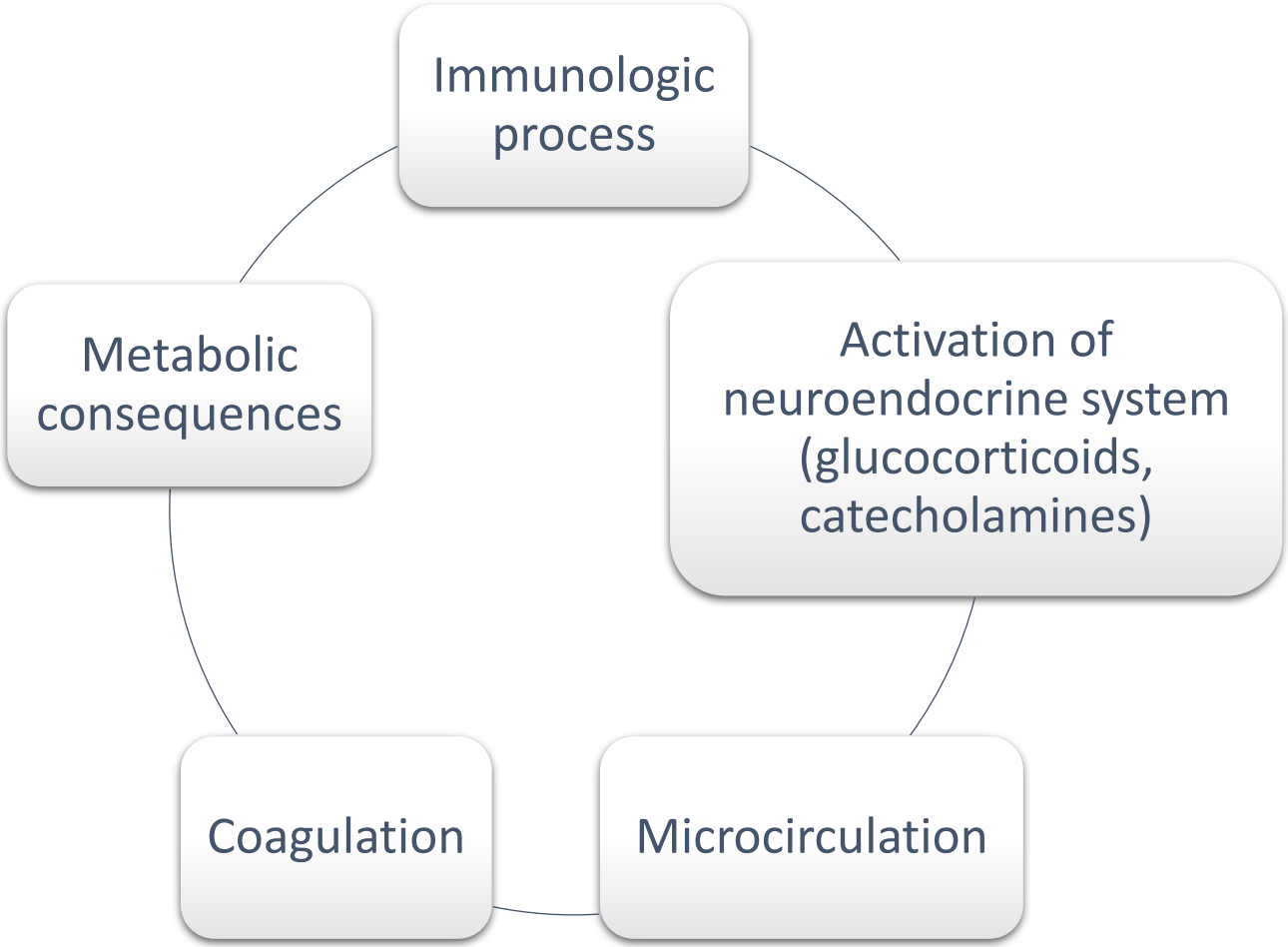
Patients who experienced longer period under the rubble, who had compartment syndrome, and underwent fasciotomy before ICU admission were more likely to have positive cultures.

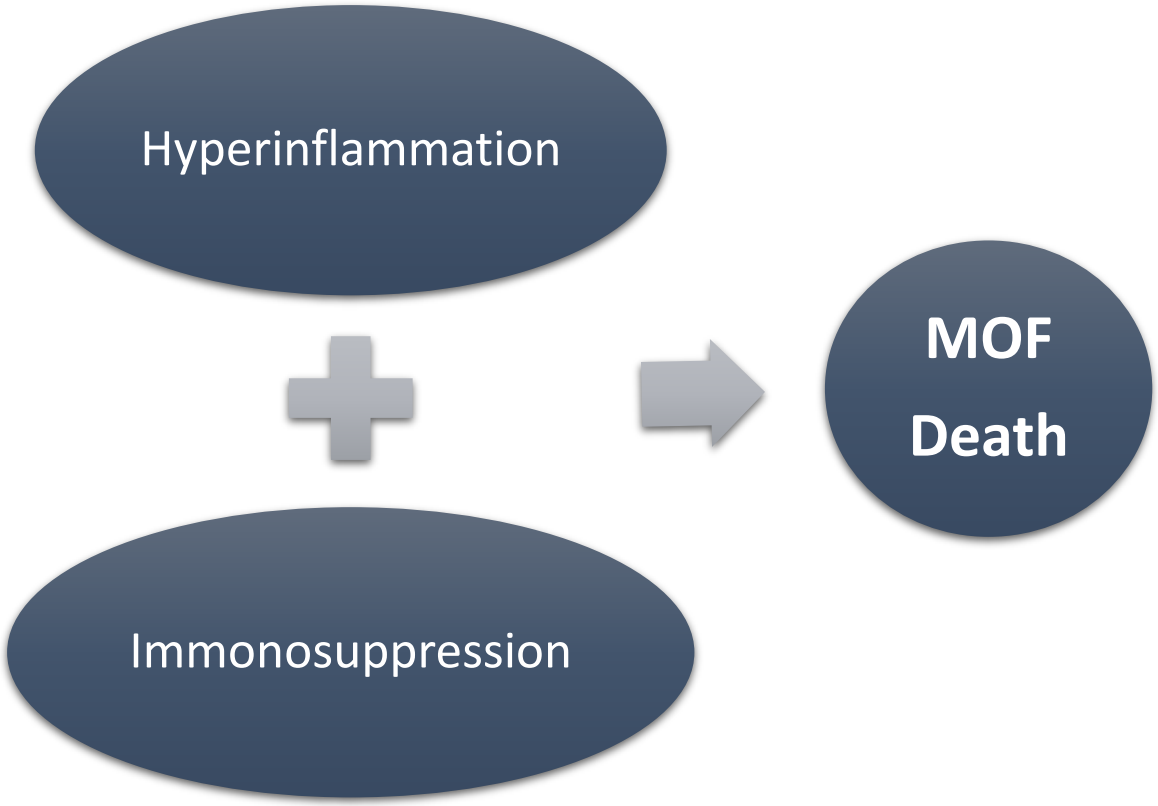
Summary

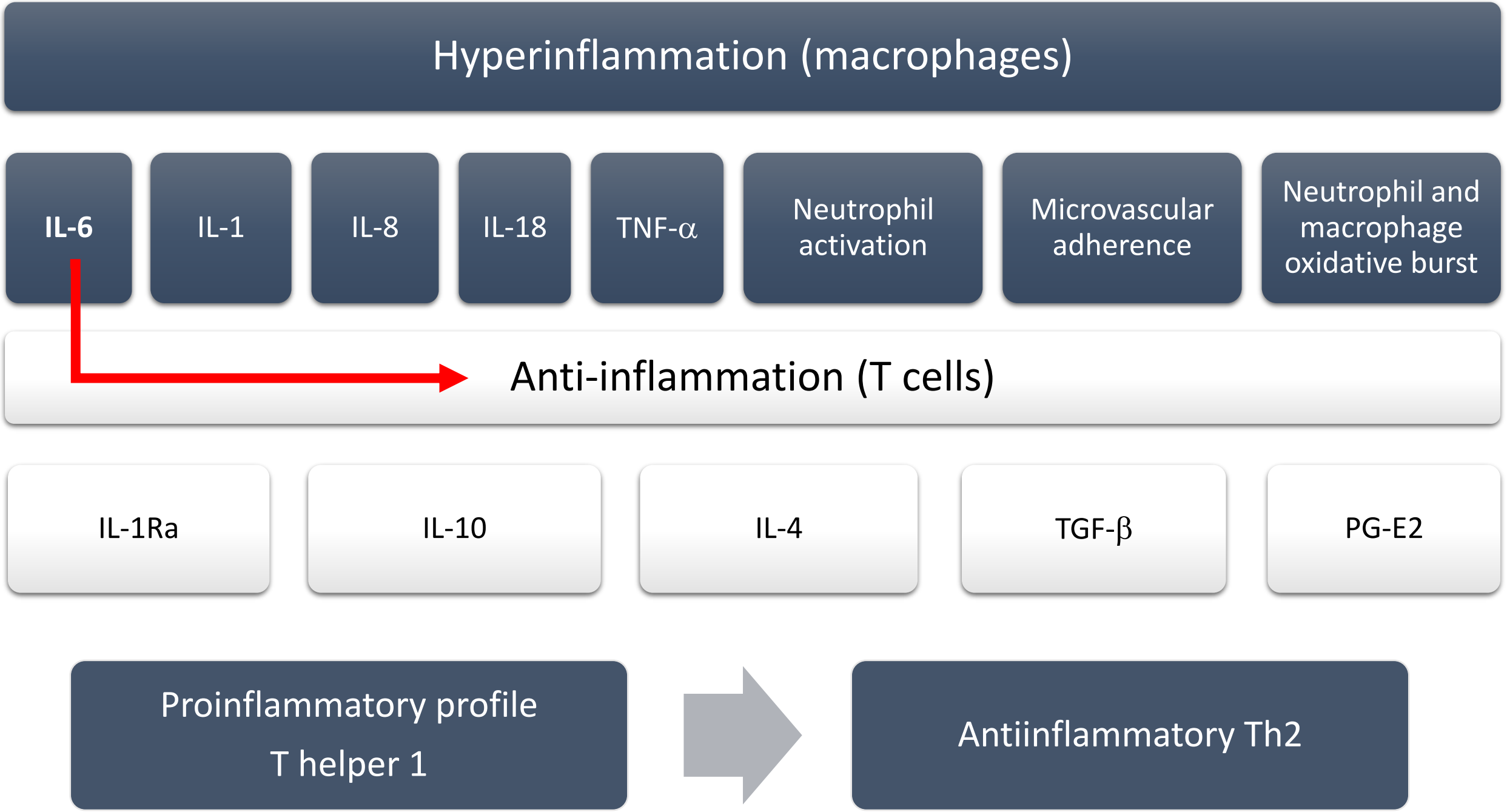
Amputation history and administration of intermittent hemodialysis before ICU admission were identified as independent variables for predicting culture positivity.

ROC curve for positive culture demonstrated that time stuck under the rubble ≥ 11.5 hours had AUC 0.64 [0.53-0.75] (p=0.019).

Trauma pathophysiology



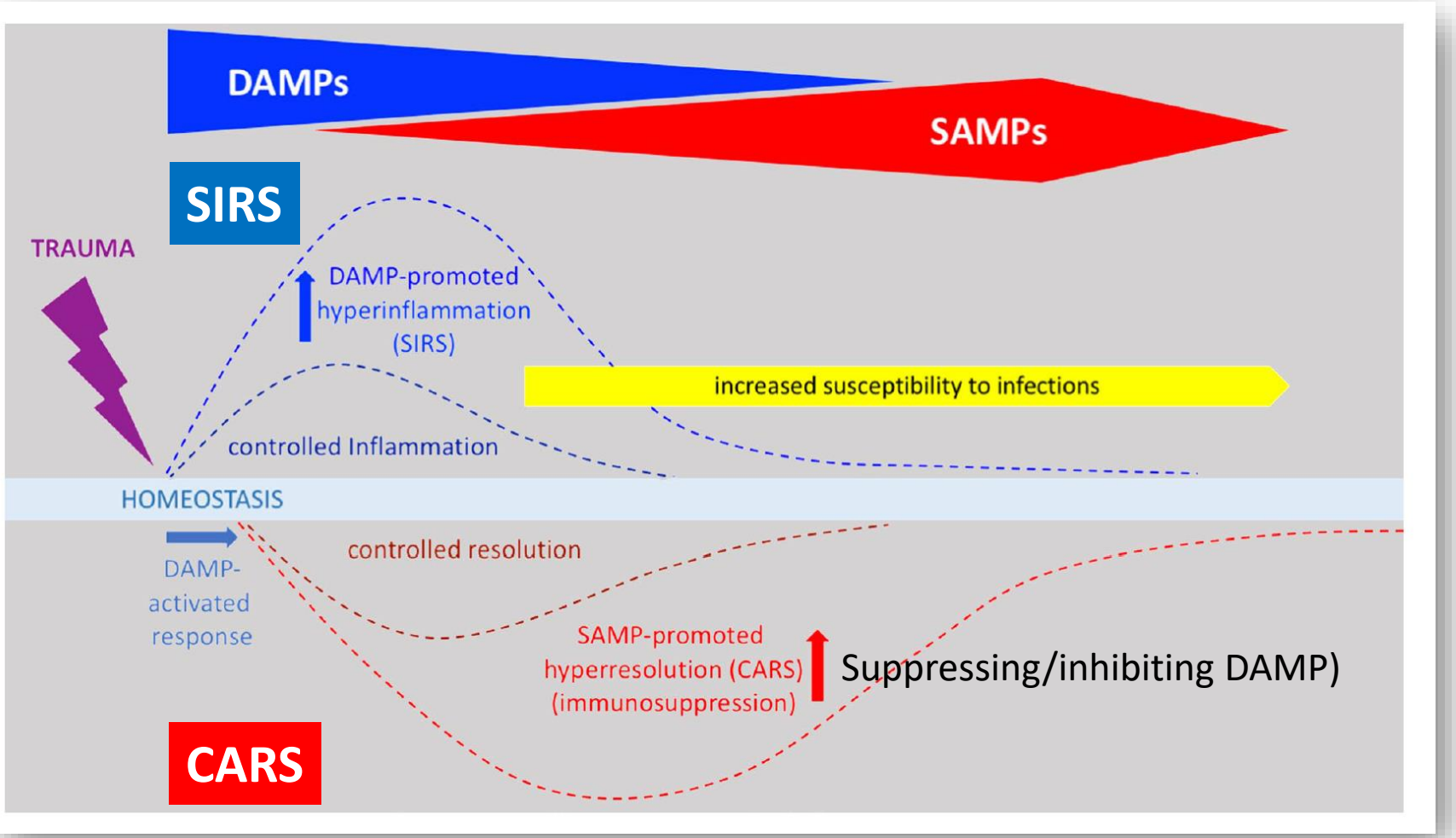


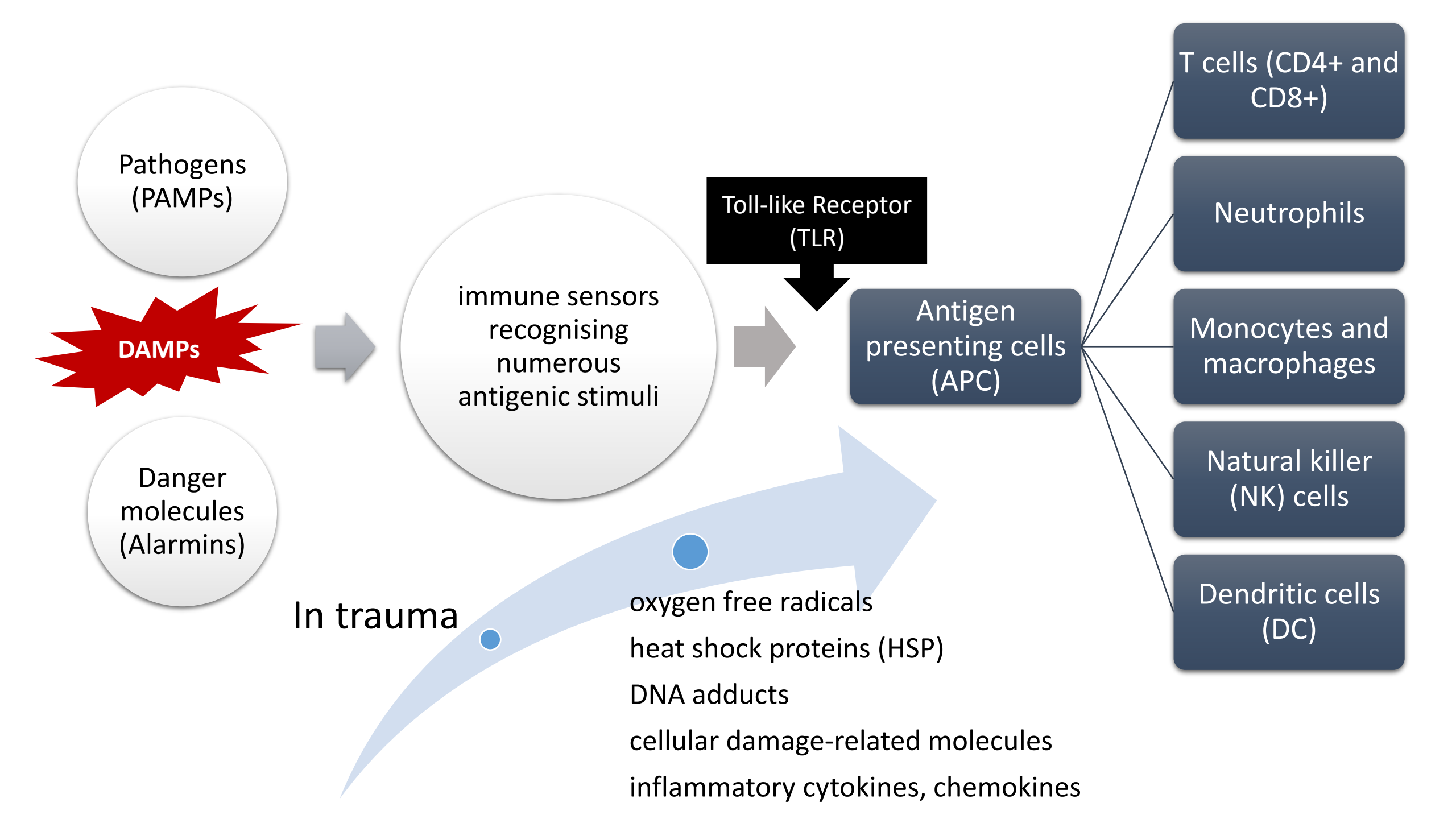

Hyperinflammation (macrophages)
IL-6
IL-1
IL-8
IL-18
TNF-α
Neutrophil activation
Microvascular adherence
Neutrophil and macrophage oxidative burst
Anti-inflammation (T cells)
IL-1Ra
IL-10
IL-4
TGF-β
PG-E2
Proinflammatory profile
T helper 1
Antiinflammatory Th2

Damage-associated molecular patterns in trauma

European Journal of Trauma and Emergency Surgery (2020) 46:751–775

Borna Relja[1,2] · Walter Gottlieb Land[3]

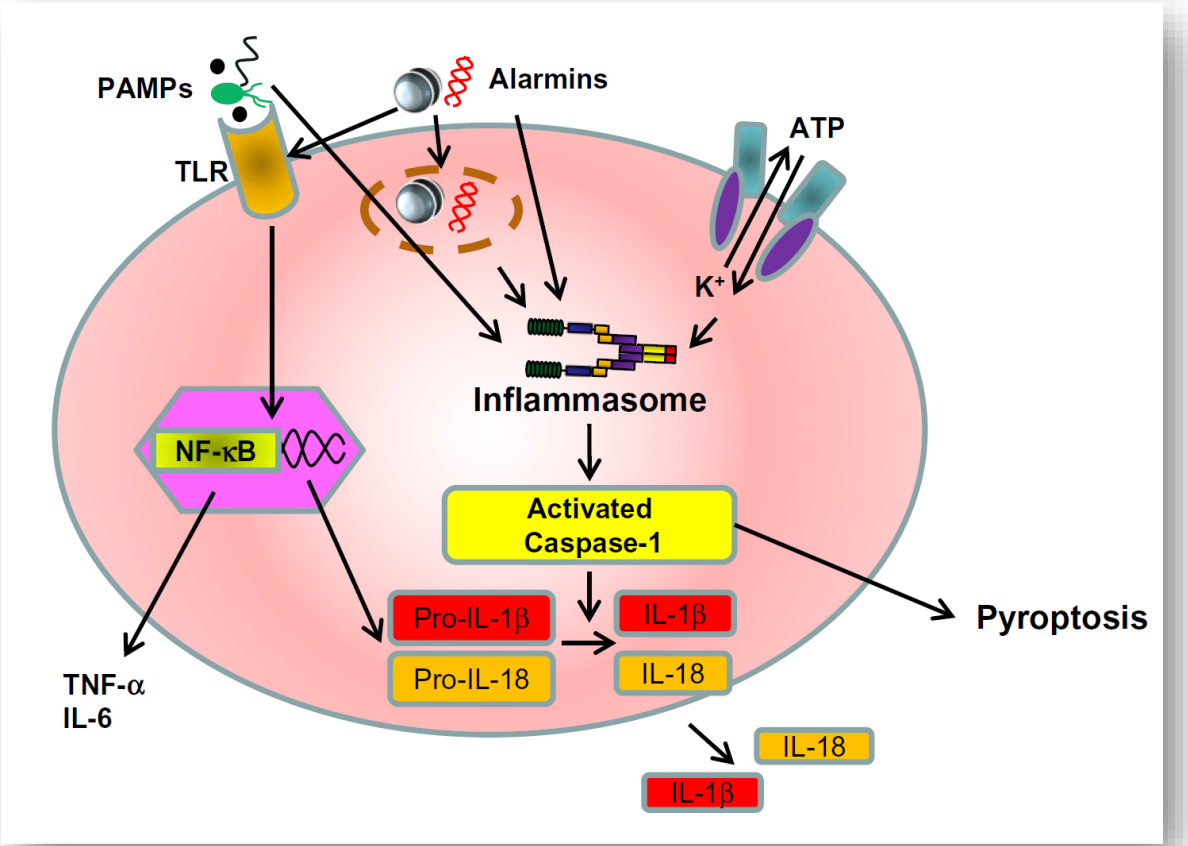


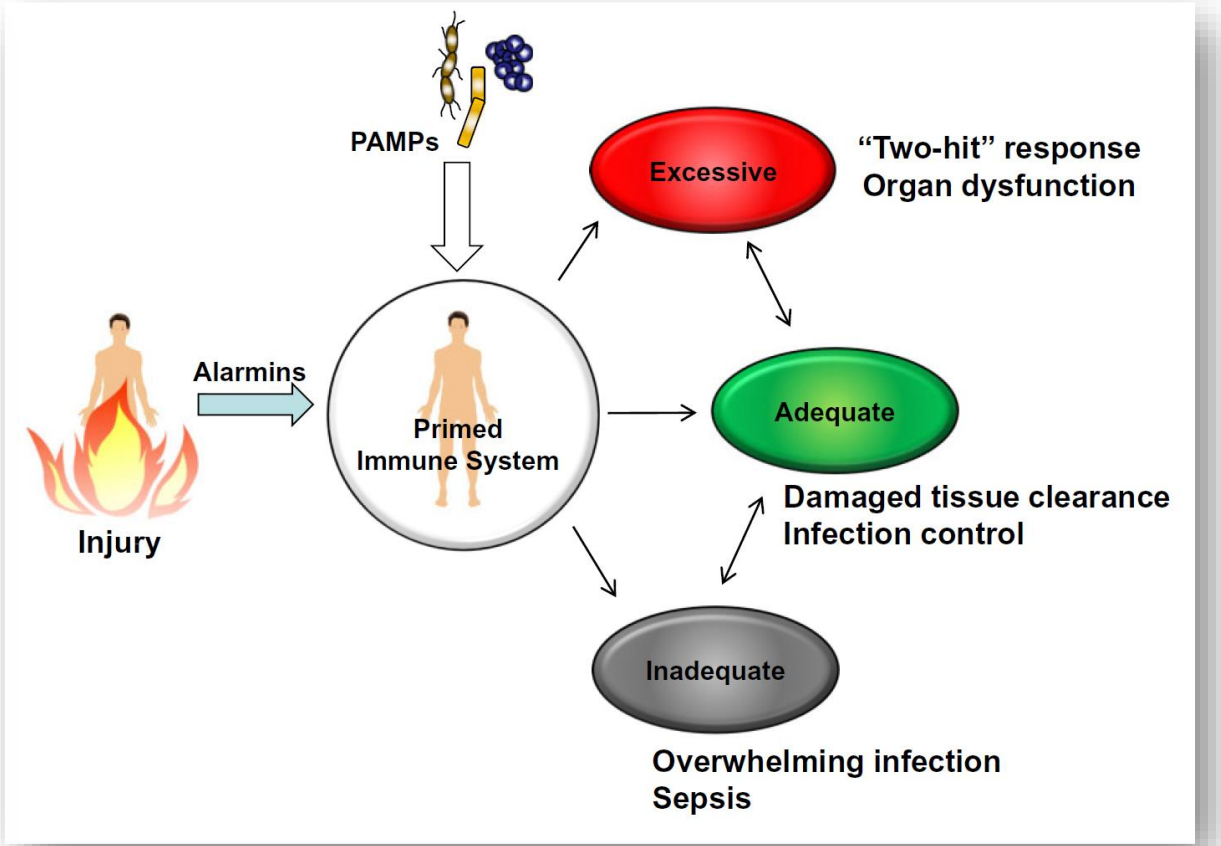

Pathogens (PAMPs)
DAMPs
Danger molecules (Alarmins)
immune sensors recognising numerous antigenic stimuli
Toll-like Receptor (TLR)
Antigen presenting cells (APC)
T cells (CD4+ and CD8+)
Neutrophils
Monocytes and macrophages
Natural killer (NK) cells
Dendritic cells (DC)
In trauma
oxygen free radicals
heat shock proteins (HSP)
DNA adducts
cellular damage-related molecules
inflammatory cytokines, chemokines

Immune response to traumatic injury: harmony and discordance of immune system homeostasis

Acute Medicine & Surgery 2014; **1**: 63–69

Akinori Osuka,[1,2,3] Hiroshi Ogura,[2] Masashi Ueyama,[1] Takeshi Shimazu,[2] and James A. Lederer[3]

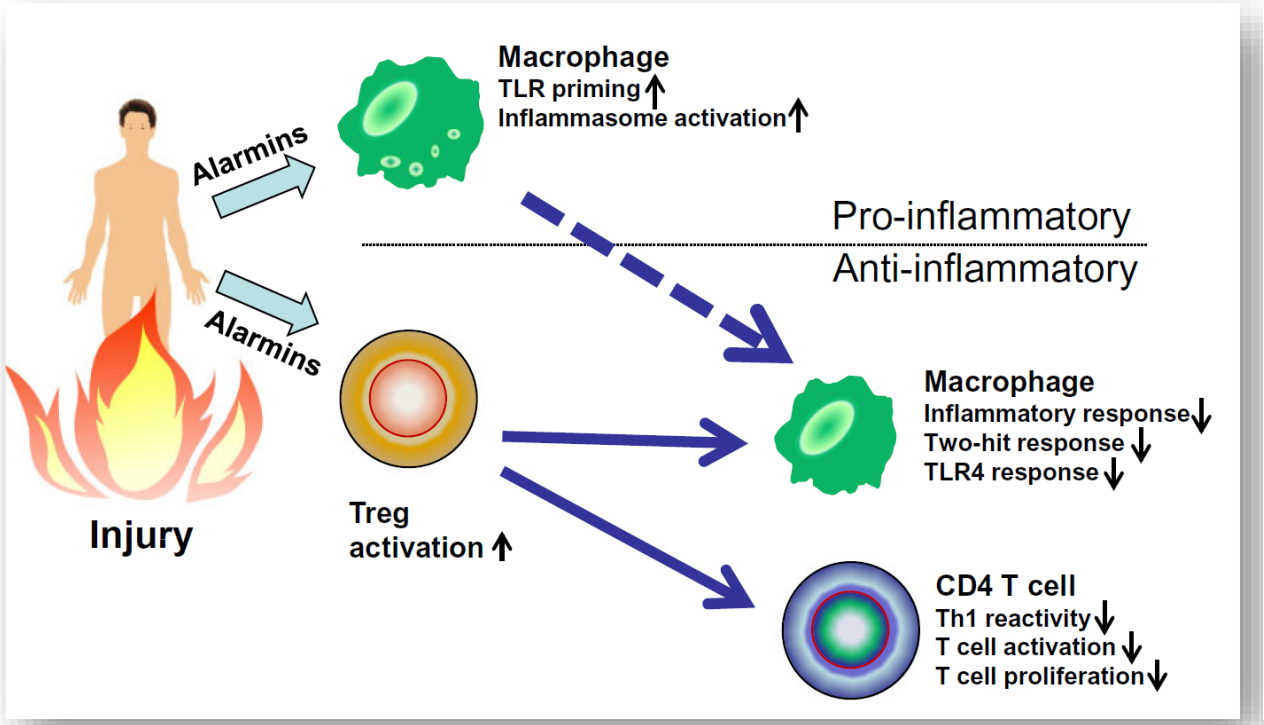


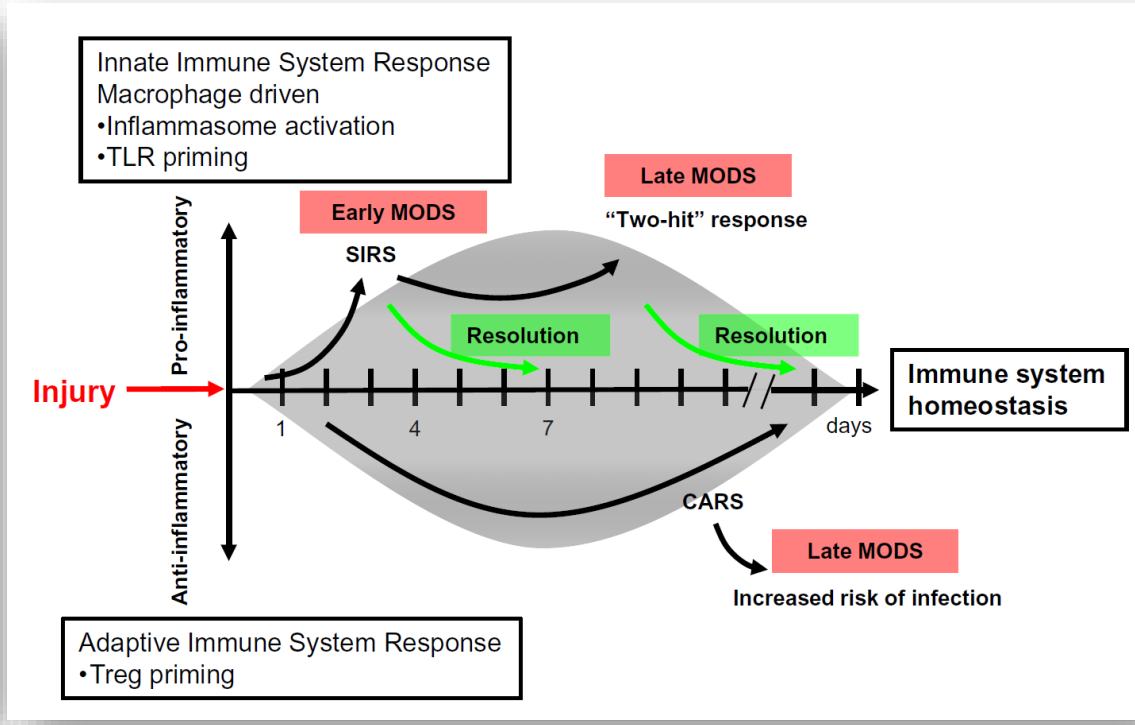


Immune response to traumatic injury: harmony and discordance of immune system homeostasis

Acute Medicine & Surgery 2014; **1**: 63–69

Akinori Osuka,[1,2,3] Hiroshi Ogura,[2] Masashi Ueyama,[1] Takeshi Shimazu,[2] and James A. Lederer[3]





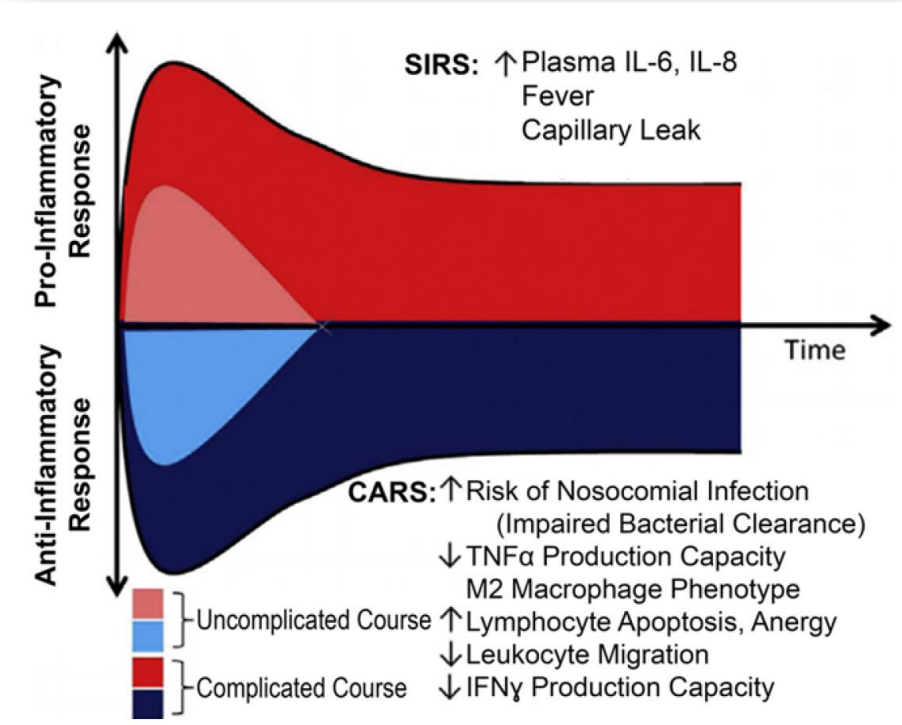
Central nervous system injury–induced immune suppression

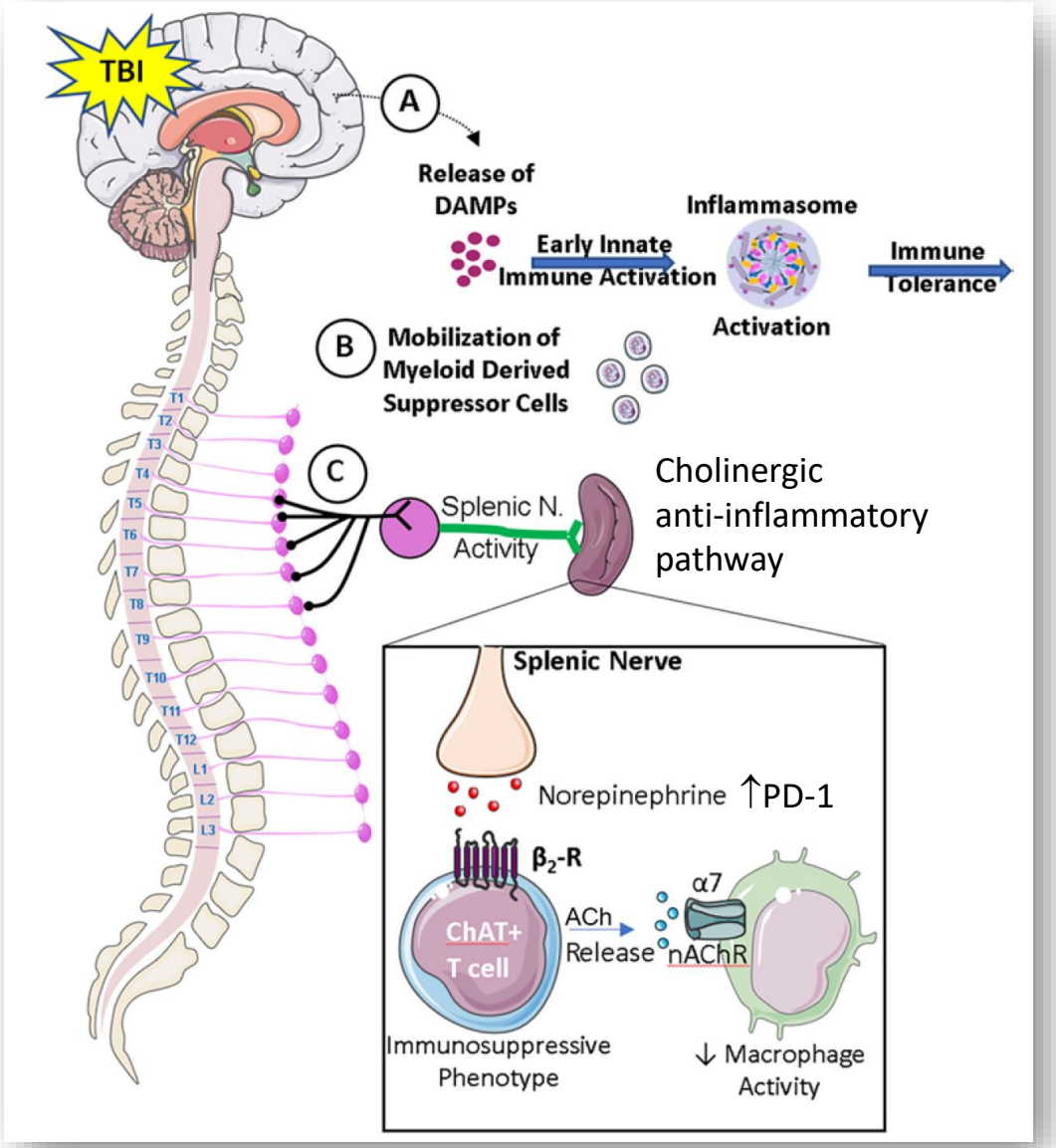
Neurosurg Focus 52 (2):E10, 2022

Eric A. Sribnick, MD, PhD,[1,2] Phillip G. Popovich, PhD,[3–6] and Mark W. Hall, MD[2,7]

Traumatic brain injury increases HAI rate by 2x as compared to non-traumatic injury within first 3 days.

HAI rate 50%, mortality 37%.

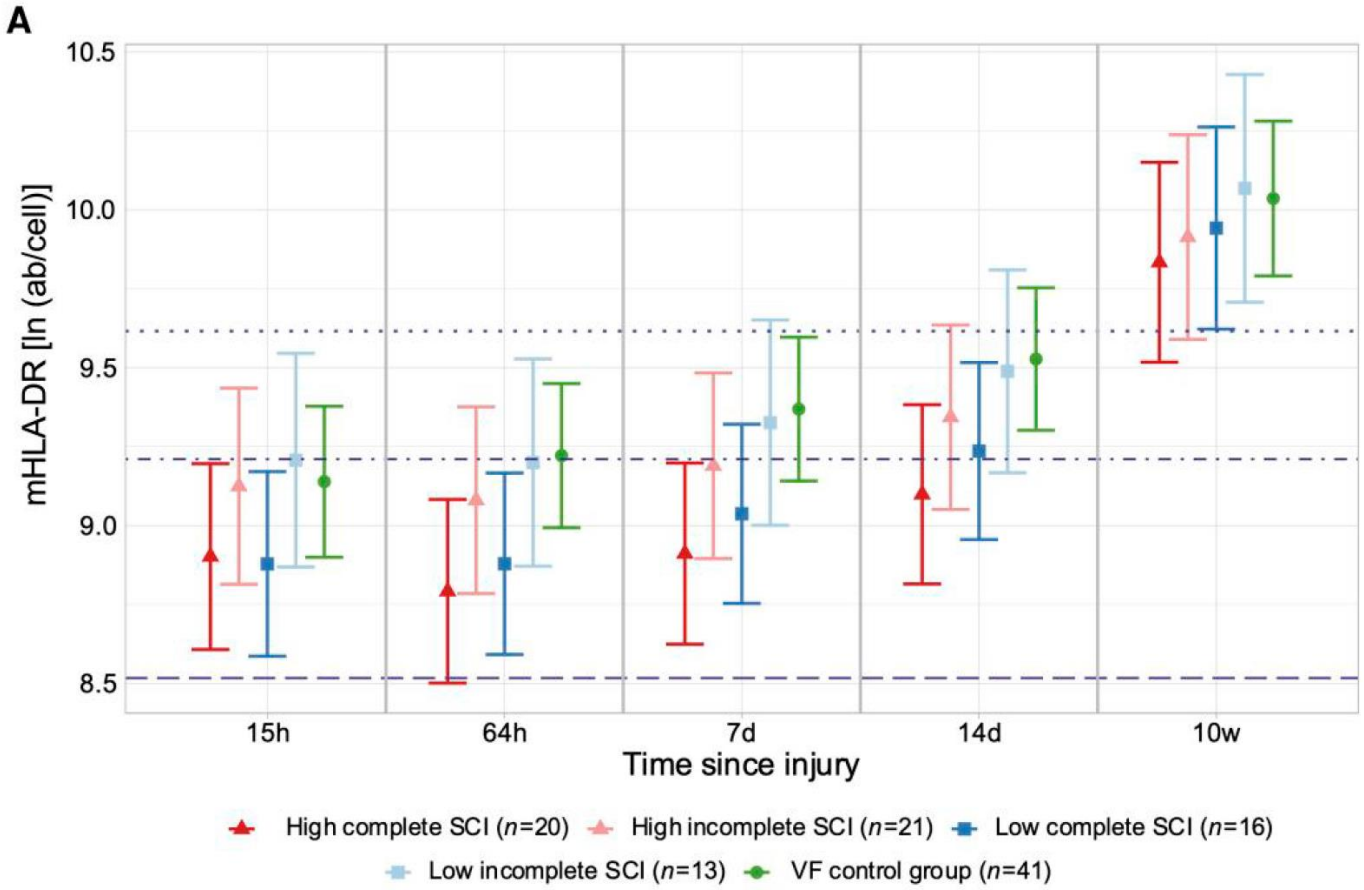


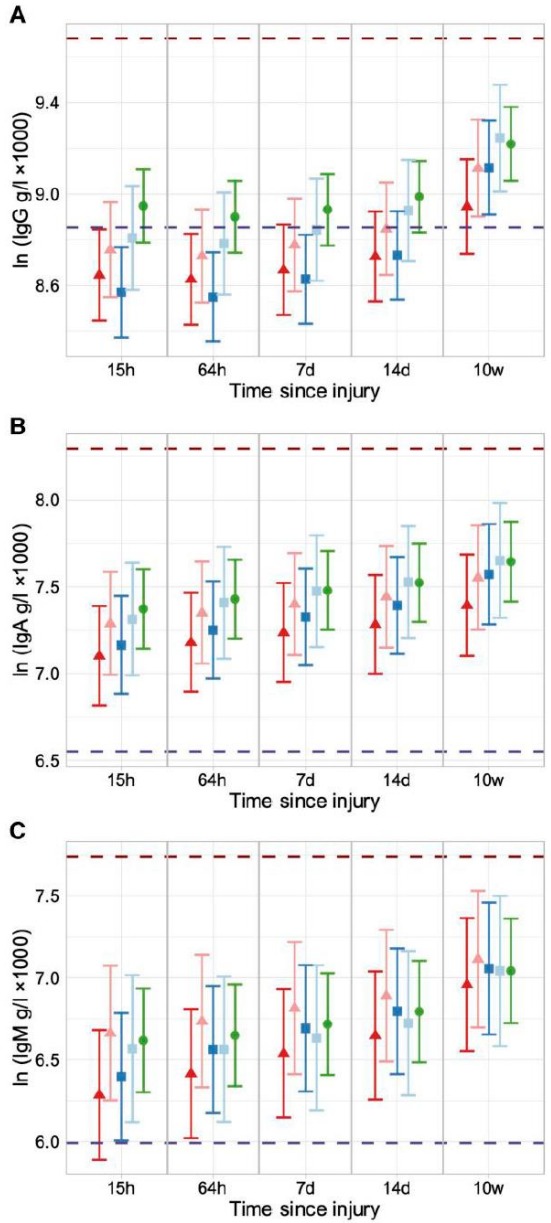


The spinal cord injury-induced immune deficiency syndrome: results of the SCIentinel study

BRAIN 2023: 146; 3500–3512

Marcel A. Kopp,[1,2,3,†] Christian Meisel,[4,5,6,†] Thomas Liebscher,[7,†] Ralf Watzlawick,





So …

- Infections will continue to be a challenge
  - Antimicrobial resistance
  - Pandemics
  - Disasters (very high rate of MDR microorganisms)
- There is no clinical evidence for a pharmacologic treatment of immunedysregulation in trauma
- Long way to go in the management of challenging infections and traume induced immunedysregulation !

Thank you …

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