SITA
Società Italiana di Terapia Antinfettiva
Antibatterica Antivirale Antifungina

12° CONGRESSO NAZIONALE

CATANIA | 17-18 novembre 2022

Infezioni addominali complicate: approccio multi specialistico

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Complicated & Uncomplicated IAI

Solomkin JS et al. Clin Infect Dis 2010; 50: 133-164

Complicated IAI

- Extension beyond the hollow viscus of origin
- Peritoneal involvement
- Associated with abscess formation or peritonitis

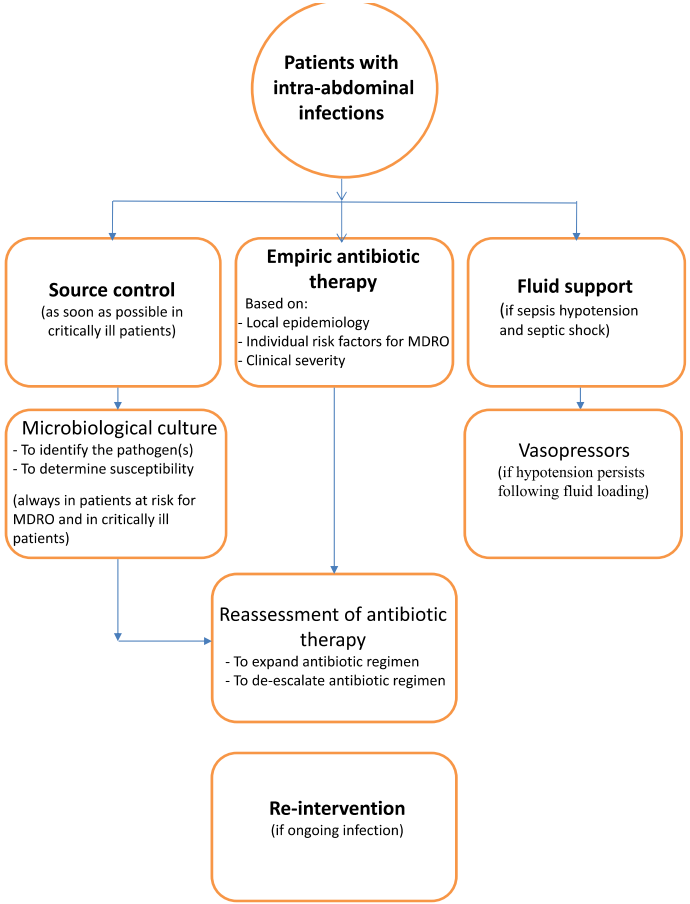
Uncomplicated IAI

- Intramural inflammation of the GI tract
- With a probability of progressing to cIAI

Management of IAI

modified from Marshall Crit Care Med 2003

Sartelli et al W Journ Emerg Surg 2021



1 Principles of management of IAIs

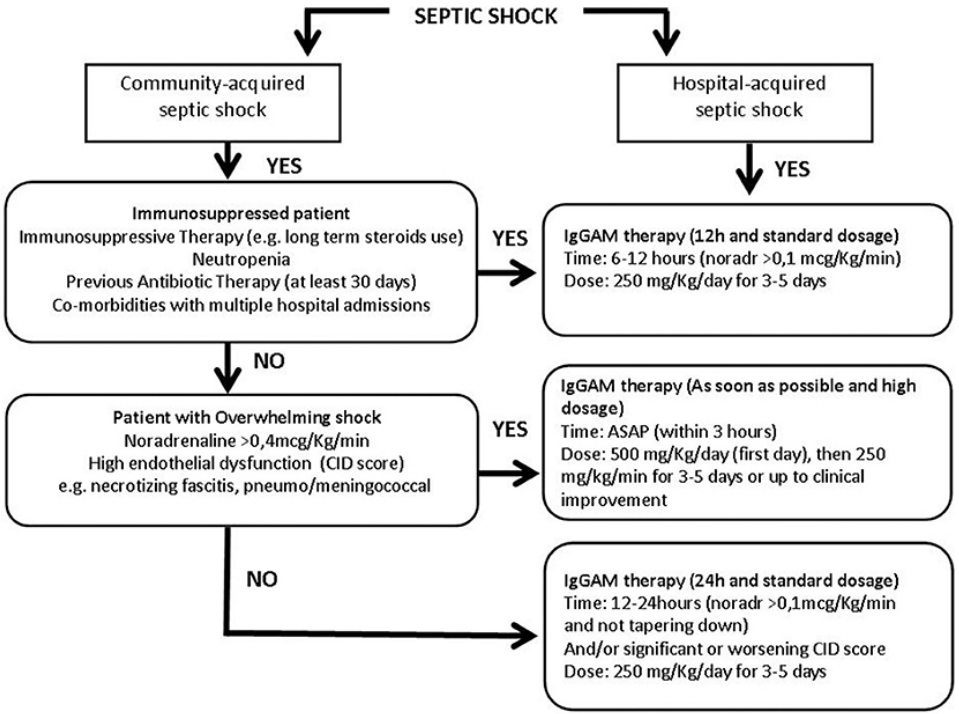
Adjunctive Immunotherapy With Polyclonal Ig-M Enriched Immunoglobulins for Septic Shock: From Bench to Bedside. The Rationale for a Personalized Treatment Protocol

Busani et al Frontiers Lausanne 2021

Epidemiology

Patient

Severity of disease



Dosage

Timing

New Microbiologica, 42, 3, 176-180, 2019, ISSN 1121-7138

FULL PAPER

A Position Paper on IgM-Enriched Intravenous Immunoglobulin Adjunctive Therapy in Severe Acute Bacterial Infections: The TO-PIRO SCORE Proposal

Francesco Giuseppe De Rosa[1], Silvia Corcione[1], Carlo Tascini[2], Daniela Pasero[3], Andrea Rocchetti[4], Massimo Massaia[5], Giorgio Berlot[6], Paolo Solidoro[7*], Massimo Girardis[8]

Table 1 - *Evaluation criteria of the TO-PIRO score.*

Items	*Criteria*	*Score*
Predisposition	• Uncontrolled cancer	1
	• Colonization by MDR bacteria and/or candida	1
	• Neutropenia or immunosuppressive drugs (monoclonal/steroids/micophenolate/cyclosporin) or allogenic stem cell transplant or splenectomy	2
Insult	• Necrotizing fasciitis, invasive meningococcal/ pneumococcal diseases, *Streptococcus pyogenes*; CA-MRSA	5
	• MDR infections or nosocomial infections	2
	• Secondary/tertiary peritonitis	2
Response	• Leucocytes < 600/ul	2
	• IgM < 60 mg/dl	2
	• PCT > 10 ng/l and CRP >20 mg/dl	1
	• PCT > 100 ng/l or endotoxin > 0.6 or IL-6>1000 pg/ml or adrenomedullin > 4 nm/l *or* presepsin 1400 ng/l	2
	• Disseminated intravascular coagulation	1
Organ	• Septic shock	3
	• Sepsis with ≥ 1 organ failure	2
	• Infection without sepsis	1

CA-MRSA, methicillin-resistant *Staphylococcus aureus*; CRP, C-reactive protein; IgM, immunoglobulins M; IL, interleukin; MDR, multi-drug resistant; PCT, procalcitonin.

Clinical Infectious Diseases

IDSA GUIDELINE

Clin Infect Dis 2010;50:133-64

Diagnosis and Management of Complicated Intra-abdominal Infection in Adults and Children: Guidelines by the Surgical Infection Society and the Infectious Diseases Society of America

Joseph S. Solomkin,[1] John E. Mazuski,[2] John S. Bradley,[3] Keith A. Rodvold,[7,8] Ellie J. C. Goldstein,[5] Ellen J. Baron,[6] Patrick J. O'Neill,[9] Anthony W. Chow,[16] E. Patchen Dellinger,[10] Soumitra R. Eachempati,[11] Sherwood Gorbach,[12] Mary Hilfiker,[4] Addison K. May,[13] Avery B. Nathens,[17] Robert G. Sawyer,[14] and John G. Bartlett[15]

IV. WHAT ARE THE PROPER PROCEDURES FOR OBTAINING ADEQUATE SOURCE CONTROL?

11. An appropriate source control procedure to drain infected foci, control ongoing peritoneal contamination by diversion or resection, and restore anatomic and physiological function to the extent feasible is recommended for nearly all patients with intra-abdominal infection (B-II).

12. Patients with diffuse peritonitis should undergo an emergency surgical procedure as soon as is possible, even if ongoing measures to restore physiologic stability need to be continued during the procedure (B-II).

Bloos *et al. Critical Care* 2014, **18**:R42
http://ccforum.com/content/18/2/R42

CRITICAL CARE

RESEARCH Open Access

Impact of compliance with infection management guidelines on outcome in patients with severe sepsis: a prospective observational multi-center study

Studio osservazionale prospettico multicentrico
Setting: ICU, sepsi severa-shock settico
1011 pts
Source control (SC) > 6 h : mortalità: 42.9% vs 26.7% (p<0.001)
Source control precoce associato a riduzione di mortalità

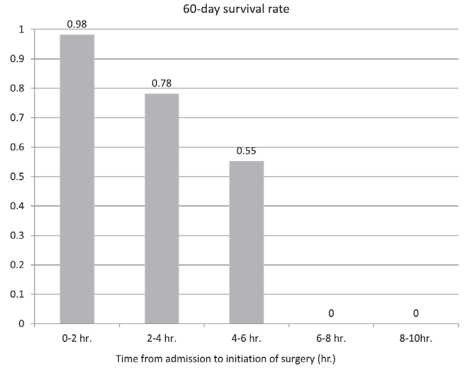
Azuhata *et al. Critical Care* 2014, **18**:R87
http://ccforum.com/content/18/3/R87

CRITICAL CARE

RESEARCH Open Access

Time from admission to initiation of surgery for source control is a critical determinant of survival in patients with gastrointestinal perforation with associated septic shock

Takeo Azuhata[1*], Kosaku Kinoshita[1], Daisuke Kawano[1], Tomonori Komatsu[1], Atsushi Sakurai[1], Yasutaka Chiba[2] and Katsuhisa Tanjho[1]



Results: Logistic regression analysis demonstrated that time to initiation of surgery (hours) was significantly associated with 60-day outcome (Odds ratio (OR), 0.31; 95% Confidence intervals (CI)), 0.19-0.45; *P* <0.0001). Time to initiation of surgery (hours) was selected as an independent factor for 60-day outcome in multiple logistic regression analysis (OR), 0.29; 95% CI, 0.16-0.47; *P* <0.0001). The survival rate fell as surgery initiation was delayed and was 0% for times greater than 6 hours.

Trial of Short-Course Antimicrobial Therapy for Intraabdominal Infection

Sawyer et al. NEJM 2015

- Rct 518 patients with IAI and adequate source control:
- Receive antibiotics until 2 days after the resolution of fever, leukocytosis, and ileus, with a maximum of 10 days of therapy (control group), or to receive a fixed course of antibiotics (experimental group) for 4±1 calendar days

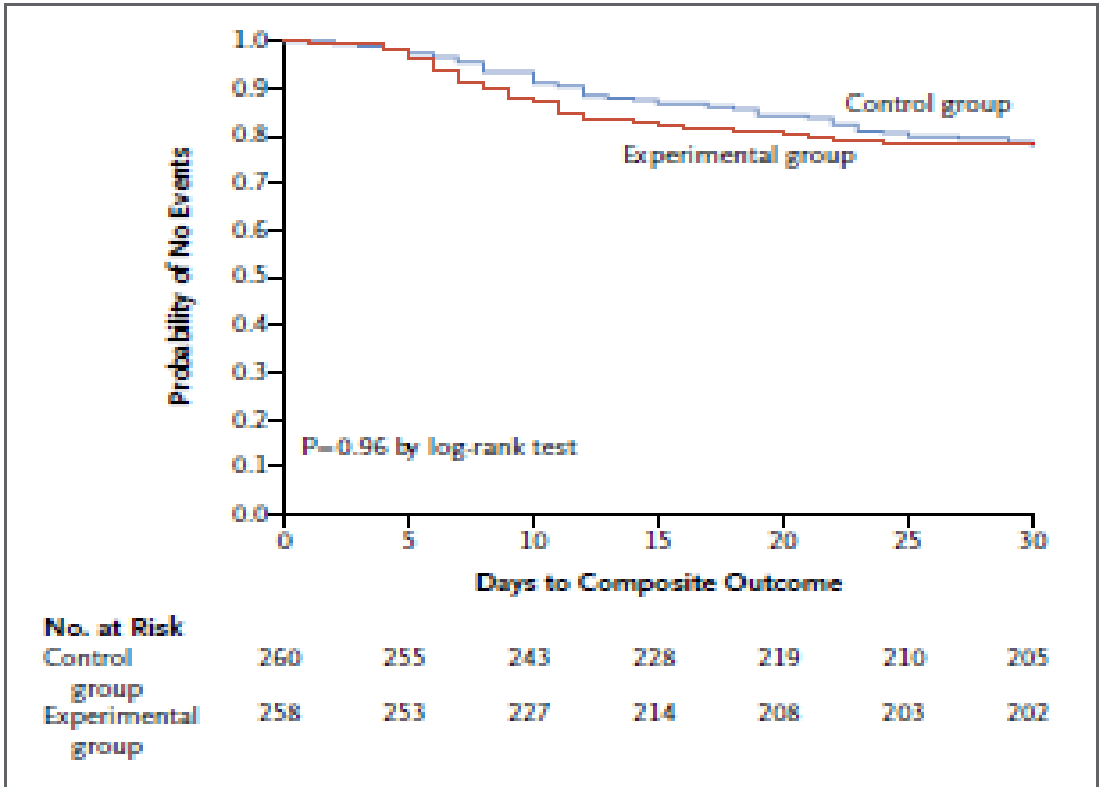
Table 1. Baseline Demographic and Clinical Characteristics, According to Study Group.*

Variable	Control Group (N = 260)	Experimental Group (N = 258)
Age — yr	52.2±1.0	52.2±1.0
Male sex — no. (%)	145 (55.8)	144 (55.8)
Race or ethnic group — no. (%)†		
White	208 (80.0)	196 (76.0)
Black	43 (16.5)	51 (19.8)
Asian	5 (1.9)	6 (2.3)
American Indian or Alaskan Native	2 (0.8)	1 (0.4)
Hispanic — no. (%)	20 (7.7)	15 (5.8)
Other	2 (0.8)	4 (1.6)
Characteristics of index infection		
APACHE II score‡	9.9±0.4	10.3±0.4
Maximum white-cell count — per mm^3	15,600±0.4	17,100±0.7
Maximum body temperature — °C	37.8±0.1	37.7±0.1
Organ of origin — no. (%)		
Colon or rectum	80 (30.8)	97 (37.6)
Appendix	34 (13.1)	39 (15.1)
Small bowel	31 (11.9)	42 (16.3)
Source-control procedure — no. (%)		
Percutaneous drainage	86 (33.1)	86 (33.3)
Resection and anastomosis or closure	69 (26.5)	64 (24.8)
Surgical drainage only	55 (21.2)	54 (20.9)
Resection and proximal diversion	27 (10.4)	37 (14.3)
Simple closure	20 (7.7)	12 (4.7)
Surgical drainage and diversion	3 (1.2)	4 (1.6)

Trial of Short-Course Antimicrobial Therapy for Intraabdominal Infection

Sawyer et al. NEJM 2015

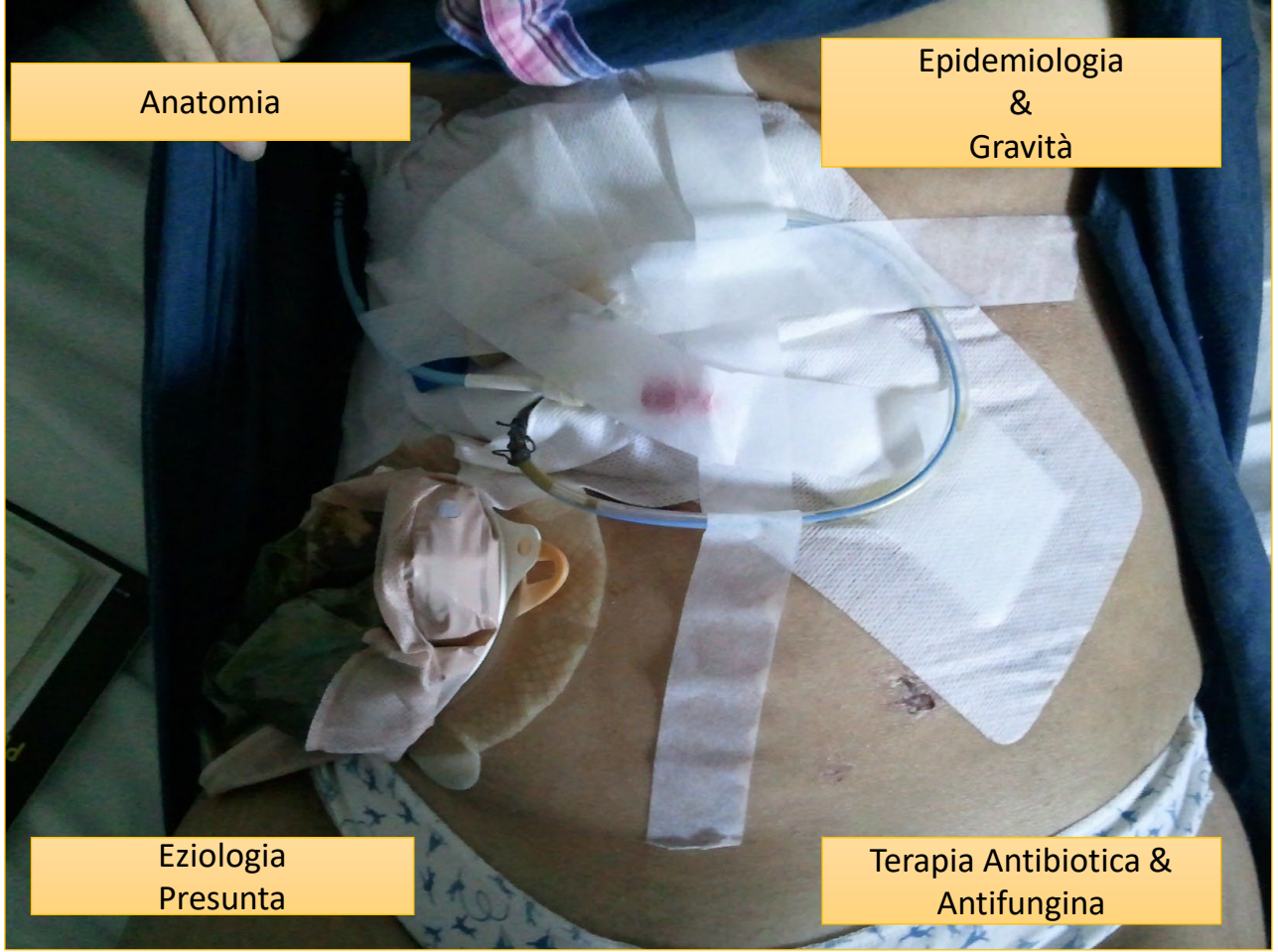
- Composite outcome:
  - -Recurrent IAI
  - -Surgical site infection
  - -Death



No. at Risk							
Control group	260	255	243	228	219	210	205
Experimental group	258	253	227	214	208	203	202

Criteria for Selection of an Antimicrobial cIAI

- Patient characteristics
  - Prior antibiotic therapy & Epidemiology: CA Vs HA
- Etiology and risk factors for etiology or resistance
  - Gram-negatives Vs Enterococci
  - Enterococci Vs Pseudomonas / Acinetobacter
- Pharmakokinetics/pharmakodynamics
  - Dosage & Infusion
- Antibiotic stewardship protocols
  - Carba-sparing strategies
  - Local epidemiology


Anatomia
Epidemiologia
&
Gravità
Eziologia
Presunta
Terapia Antibiotica &
Antifungina

Essentials for Selecting Antimicrobial Therapy for IAIs

Blot S et al Drugs 2012

- Confusion derived from «complicated» & «uncomplicated»
- Tertiary peritonitis unreliable
  - Only indicates failure of treatment of secondary peritonitis
- A grid is proposed
  - (i) Anatomical disruption
  - (ii) Severity of disease expression
  - (iii) Epidemiology or recent antibiotic exposure

Epidemiology & Abdominal Infections

Blot S et al Drugs 2012

Baseline Coverage	Nosocomial Gram-negative Bacteria	Enterococci Candida
1	2	2 / 3

CA → HC → HA

The «Grid»

Blot S et al Drugs 2012

	Disease Expression		
	Mild (Sepsis)	Moderate (Severe Sepsis)	Severe (Septic Shock)
Community-acquired or early-onset healthcare-associated IAI < 7 days after hospital admission			
Without perforation	1	1	2
Localized peritonitis	1	1	2
Diffuse peritonitis	1	2	2

	Disease Expression		
	Mild (Sepsis)	Moderate (Severe Sepsis)	Severe (Septic Shock)
Late-onset healthcare-associated IAI (≥7days after hospital admission) and/or recent antimicrobial exposure			
Without perforation	2	2	2
Localized peritonitis	2	2	3
Diffuse peritonitis	2	3	3

Community-acquired IAIs

Sartelli M et al WJES 2021

	Risk factors for ESBL	Treatment	Treatment
Stable, non-critical	No	Amox / Clav **Ceftriaxone+ metro** **Cefotaxime+ metro**	Cipro + Metro
	Yes	Ertapenem **tigecyline**	-
Critically ill (≥ severe sepsis)	No	Pip / Tazo **Cefepime+ metro**	-
	Yes	Mero / Imi	+ / - Fluco

Emphasis on:
The role of tigecycline monotreatment (2h infusion time)
Choice of antibiotics and its administration
Amox / Clav: 2.2g q6h (2-hour infusion time)
Pip / Tazo : 8 / 2 g Loading Dose and then 16 / 4 g continuous infusion or 4.5g q6h
Meropenem: 500 mg q6h (6h infusion time)
Imipenem : 500 mg q4h (3h infusion time)

Nosocomial IAIs

Sartelli M et al WJES 2021

	Risk factors for MDR	Treatment	Treatment
Stable, non-critical	NO	Piperacillin + Tigecycline + /- Fluconazole	
Critically ill (≥ severe sepsis)	Yes	**meropenem** **Ceftolozane/taz + metro** **Caz/avi + metro** **+ vanco/teico** **+/- echinocandin**	Mer / Imi / Dori + Teico (Vanco) + Echinocandin

If risk of VRE: linezolid/ daptomycin 6mg/kg/die

Carbapenem Sparing Strategies

Corcione S. et al Curr Opin Infect Dis 2019

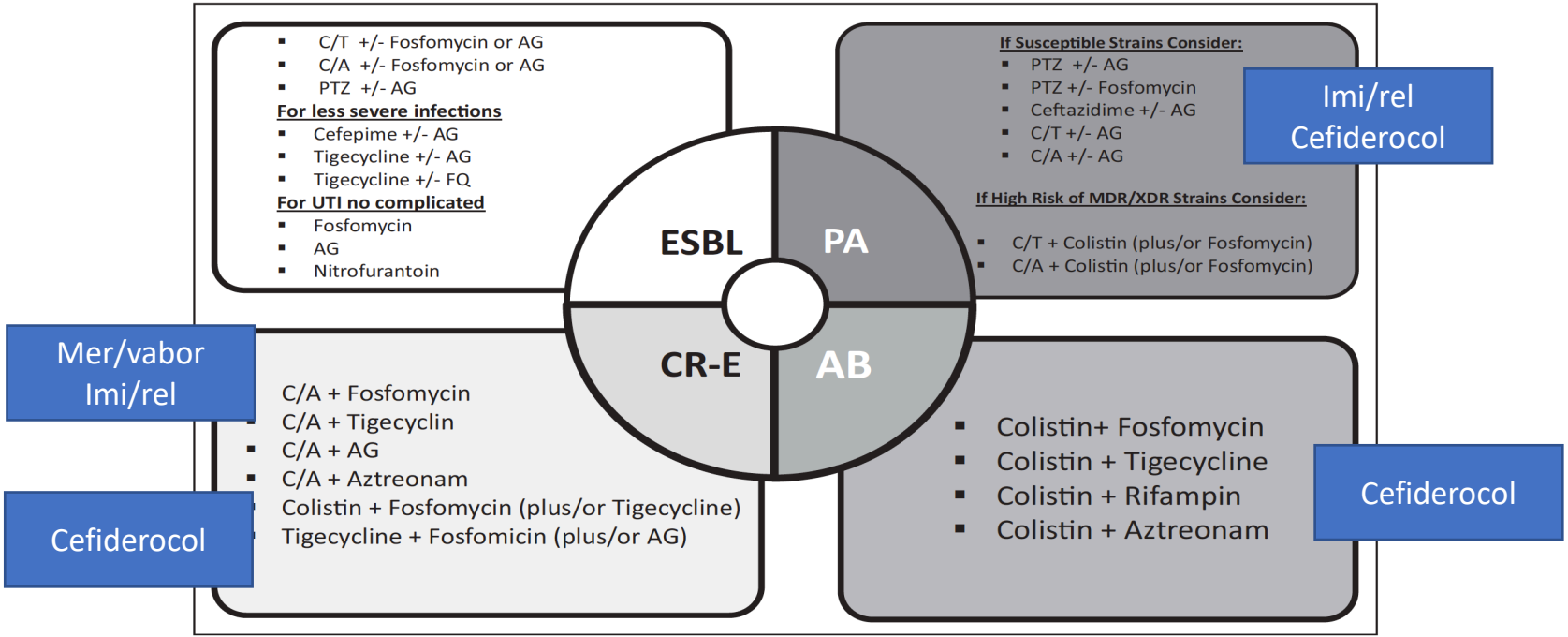


FIGURE 1. Carbapenem sparing strategies in the setting of suspected infections by extended-spectrum β-lactamase producing, *P. aeruginosa* (PA), *A. baumannii* (AB), carbapenem-resistant *Enterobacteriaceae* (CR-E). AG, aminoglycoside; C/A, ceftazdime/avibactam; C/T, ceftolozane/tazobactam; FQ, fluoroquinolones.

A Proposal for a Classification Guiding the Selection of Appropriate Antibiotic Therapy for Intra-Abdominal Infections

Sartelli et al Antibiotics 2022

Table 1. Patients with community-acquired intra-abdominal infection without sepsis or septic shock.

Empiric Antibiotic Regimens; Normal Renal Function
One of the following intravenous antibiotics: Amoxicillin/clavulanate 2.2 g q8h [1] Ceftriaxone 2 g every q24h + metronidazole 500 mg q8h Cefotaxime 2 g every 8 h + metronidazole 500 mg q8h Piperacillin/tazobactam 4 g/0.5 g q6h [2]
In patients with beta-lactam allergy, a fluoroquinolone-based regimen: Ciprofloxacin 400 mg every q8/12h + metronidazole 500 mg q8h
In patients with beta-lactam allergy, an aminoglycoside regimen: Amikacin 15–20 mg/kg q24h + metronidazole 500 q8h
In patients at high risk of infection with community-acquired ESBL-producing *Enterobacterales*, one of the following antibiotics: Tigecycline 100 mg LD, then 50 mg every q12h (carbapenem-sparing strategy) Ertapenem 1 g q24h

[1] Its use should be avoided if *Enterobacterales* local rate of resistance >20%. [2] In patients with advanced age (70 years of age or greater); presence of malignant disease; major compromise of cardiovascular, hepatic, or renal function; and/or hypoalbuminemia.

Table 2. Patients with community-acquired intra-abdominal infection with sepsis or septic shock.

Empiric Antibiotic Regimens; Normal Renal Function
One of the following intravenous antibiotics: Piperacillin/tazobactam 6 g/0.75 g LD then 4 g/0.5 g q6h or 16 g/2 g by continuous infusion.
In patients with documented beta-lactam allergy, an aminoglycoside regimen: Amikacin 15–20 mg/kg q24h + metronidazole 500 mg q8h
In patients at high risk of infection with community-acquired ESBL-producing *Enterobacterales*, one of the following antibiotics: Meropenem 1 g q8h (only in patients with septic shock) [1] Doripenem 500 mg q8h (only in patients with septic shock) [1] Imipenem/cilastatin 500 mg q6h (only in patients with septic shock)

[1] Meropenem and doripenem have no in vitro activity against enterococci that are susceptible to ampicillin.

A Proposal for a Classification Guiding the Selection of Appropriate Antibiotic Therapy for Intra-Abdominal Infections

Sartelli et al Antibiotics 2022

Table 3. Patients with hospital-acquired IAIs without sepsis or septic shock.

Empiric Antibiotic Regimens; Normal Renal Function
One of the following intravenous antibiotics: Tigecycline 100 mg LD, then 50 mg every 12 h (not active against *P. aeruginosa*) Eravacycline 1 mg/kg q12 h (not active against *P. aeruginosa*) + Piperacillin/tazobactam 4.5 q6h
In patients with documented beta-lactam allergy: Amikacin 15–20 mg/kg q24h
In patients with high risk for invasive candidiasis: + Fluconazole 800 mg LD then 400 mg every 24 h

Table 4. Patients with hospital-acquired intra-abdominal infection with sepsis or septic shock.

Empiric Antibiotic Regimens; Normal Renal Function
One of the following intravenous antibiotics: Meropenem 1 g q8h Doripenem 500 mg q8h Imipenem/cilastatin 500 mg q6h + One of the following intravenous antibiotics: Vancomycin 25–30 mg/kg LD then 15–20 mg/kg/q8 h Teicoplanin 12 mg/kg every 12 h 3 LDs then 12 mg/kg q24 h
In patients with high risk for invasive candidiasis, add one of the following antifungal agents: Caspofungin 70 mg LD, then 50 mg q24h Anidulafungin 200 mg LD, then 100 q24h Micafungin 100 mg q24h Amphotericin B liposomal 3 mg/kg q24h
In patients with suspected or proven infection with difficult-to-treat [1] non-metallo-beta-lactamase-producing *P. aeruginosa*, consider the use of antibiotic combinations with: Ceftolozane/tazobactam (1.5 g q8h), ceftazidime-avibactam (2.5 g q8h), and imipenem/cilastatin-relebactam (1.25 g q6h)
In patients with suspected or proven infection with carbapenemase-producing *K. pneumoniae* and MDR (non-metallo-beta-lactamase-producing) *P. aeruginosa*, consider the use of antibiotic combinations with: Ceftazidime-avibactam (2.5 g q8h), meropenem-vaborbactam (4 g 8qh), and imipenem/cilastatin-relebactam (1.25 g q6h)
In patients with suspected or proven infection with metallo-beta-lactamase-producing bacteria (i.e., NDM, VIM, IMP), consider the use of antibiotic combinations with: Ceftazidime-avibactam (2.5 g q8h) + aztreonam (2 g q8h) or cefiderocol (2 g q8h)
In patients with suspected or proven infection with vancomycin-resistant enterococci (VRE)—including patients with previous enterococcal infection or colonisation, immunocompromised patients, patients with long ICU stay, or patients with recent vancomycin exposure—consider the use of antibiotic combinations with: Linezolid (600 q 12h) or daptomycin (10–12 mg/kg q24h) [2]

[1] Difficult-to-treat is defined as *P. aeruginosa* that exhibits no susceptibility to any of the following: piperacillin/tazobactam, ceftazidime, cefepime, aztreonam, meropenem, imipenem/cilastatin, ciprofloxacin, and levofloxacin. [2] Approved at the dosage of 4 mg/kg/24 h, it is currently used at higher dosages.

Treatment in colonized patients by MDR Bacteria: KPC & MBL CRE

Sartelli et al Antibiotics 2022

Table 5. Patients with IAIs with known colonisation (infection) by KPC-producing *Enterobacterales*.

Oriented Antibiotic Regimens; Normal Renal Function
One of the following intravenous antibiotics [1]:
Ceftazidime/avibactam 2.5 g q8h + tigecycline 100 mg LD, then 50 mg every 12 h
Ceftazidime/avibactam 2.5 g q8h + metronidazole 500 mg q8h
Meropenem/vaborbactam 4 g 8qh infused in three hours
Imipenem/cilastatin/relebactam 1.25 g q6h
+
One of the following intravenous antibiotics (not for combinations with tigecycline):
Vancomycin 25–30 mg/kg LD then 15–20 mg/kg/q8 h
Teicoplanin 12 mg/kg every 12 h 3 LDs then 12 mg/kg q24 h
In patients at high risk of invasive candidiasis, add one of the following antifungal agents:
Caspofungin 70 mg LD, then 50 mg q24h
Anidulafungin 200 mg LD, then 100 q24h
Micafungin 100 mg q24h
Amphotericin B liposomal 3 mg/kg q24h

KPC: *Klebsiella pneumonia* carbapenemase. [1] The microorganism is known to be sensitive to the chosen beta-lactam.

Table 6. Patients with IAIs with known colonisation (infection) by MBL-producing *Enterobacterales*.

Oriented Antibiotic Regimens; Normal Renal Function
One of the following intravenous antibiotics:
Ceftazidime/avibactam 2.5 g q8h + aztreonam 2 g q8h + tigecycline 100 mg LD, then 50 mg every 12 h
Ceftazidime/avibactam 2.5 g q8h + aztreonam 2 g q8h + metronidazole 500 mg q8h
Cefiderocol 2 g q8h + tigecycline 100 mg LD, then 50 mg every 12 h
Cefiderocol 2 g q8h + metronidazole 500 mg q8h
In patients at high risk of invasive candidiasis, add one of the following antifungal agents:
Caspofungin 70 mg LD, then 50 mg q24h
Anidulafungin 200 mg LD, then 100 q24h
Micafungin 100 mg q24h
Amphotericin B Liposomal 3 mg/kg q24h

MBL: metallo-beta-lactamase.

Treatment in colonized patients by MDR Bacteria: PA & CRAB

Sartelli et al Antibiotics 2022

Table 7. Patients with IAIs with known colonisation by MBL-producing *P. aeruginosa*.

Oriented Antibiotic Regimens; Normal Renal Function
One of the following intravenous antibiotics: Cefiderocol 2 g q8h + tigecycline 100 mg LD, then 50 mg every 12 h Cefiderocol 2 g q8h + metronidazole 500 mg q8h Meropenem 2 g q8h + fosfomycin 4 g q6h + One of the following intravenous antibiotics (not for combinations with tigecycline or fosfomycin): Vancomycin 25–30 mg/kg LD then 15–20 mg/kg/q8 h Teicoplanin 12 mg/kg every 12 h 3 LDs then 12 mg/kg q24 h
In patients at high risk of invasive candidiasis, add one of the following antifungal agents: Caspofungin 70 mg LD, then 50 mg q24h Anidulafungin 200 mg LD, then 100 q24h Micafungin 100 mg q24h Amphotericin B liposomal 3 mg/kg q24h

MBL: metallo-beta-lactamase.

IMI/REL + AZTREONAM

Table 8. Patients with IAIs with known colonisation by carbapenem-resistant *A. baumannii*.

Oriented Antibiotic Regimens; Normal Renal Function
One of the following intravenous antibiotics: Cefiderocol 2 g q8h + tigecycline 100 mg LD, then 50 mg q12h Cefiderocol 2 g q8h + metronidazole 500 mg q8h Fosfomycin 4 g q6h + ampicillin/sulbactam 6/3 g q8h + One of the following intravenous antibiotics (not for combinations with tigecycline or fosfomycin): Vancomycin 25–30 mg/kg LD then 15–20 mg/kg/q8h Teicoplanin 12 mg/kg every 12 h 3 LDs then 12 mg/kg q24h
In patients at high risk of invasive candidiasis, add one of the following antifungal agents: Caspofungin 70 mg LD, then 50 mg q24h Anidulafungin 200 mg LD, then 100 q24h Micafungin 100 mg q24h Amphotericin B liposomal 3 mg/kg q24h

Conclusions

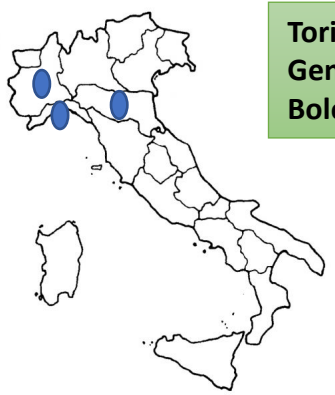
Solomkin JS et al. Clin Infect Dis 2010; Sartelli et al 2021

- Multifaceted nature of these infections
- Graded from “mild to moderate” to “more severe”
  - Scoring systems (APACHE II, others)
  - Comorbidities
  - Risk for MDR infections
- Early recognition
- Prompt physiologic stabilization using intravenous fluid therapy in critically ill patient
- Adequate source control
- Appropriate antimicrobial and antifungal therapy
  - Spectrum of coverage
  - Drugs: Role of different beta lactams
  - Dosage
  - TDM

1° Edizione Observership SITA GIOVANI

L'observership SITA giovani si rivolge ai giovani specialisti; 2 giorni di corso

- Clinico (round)
- Educativo (lezioni frontali e casi clinici)
- Ricerca clinica (progetto ricerca SITA Giovani)



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