

**XIV Congresso Brasileiro de Controle
de Infecção Hospitalar**
**Otimizando Terapia
em Pacientes Obesos**

**Novembro
2014**



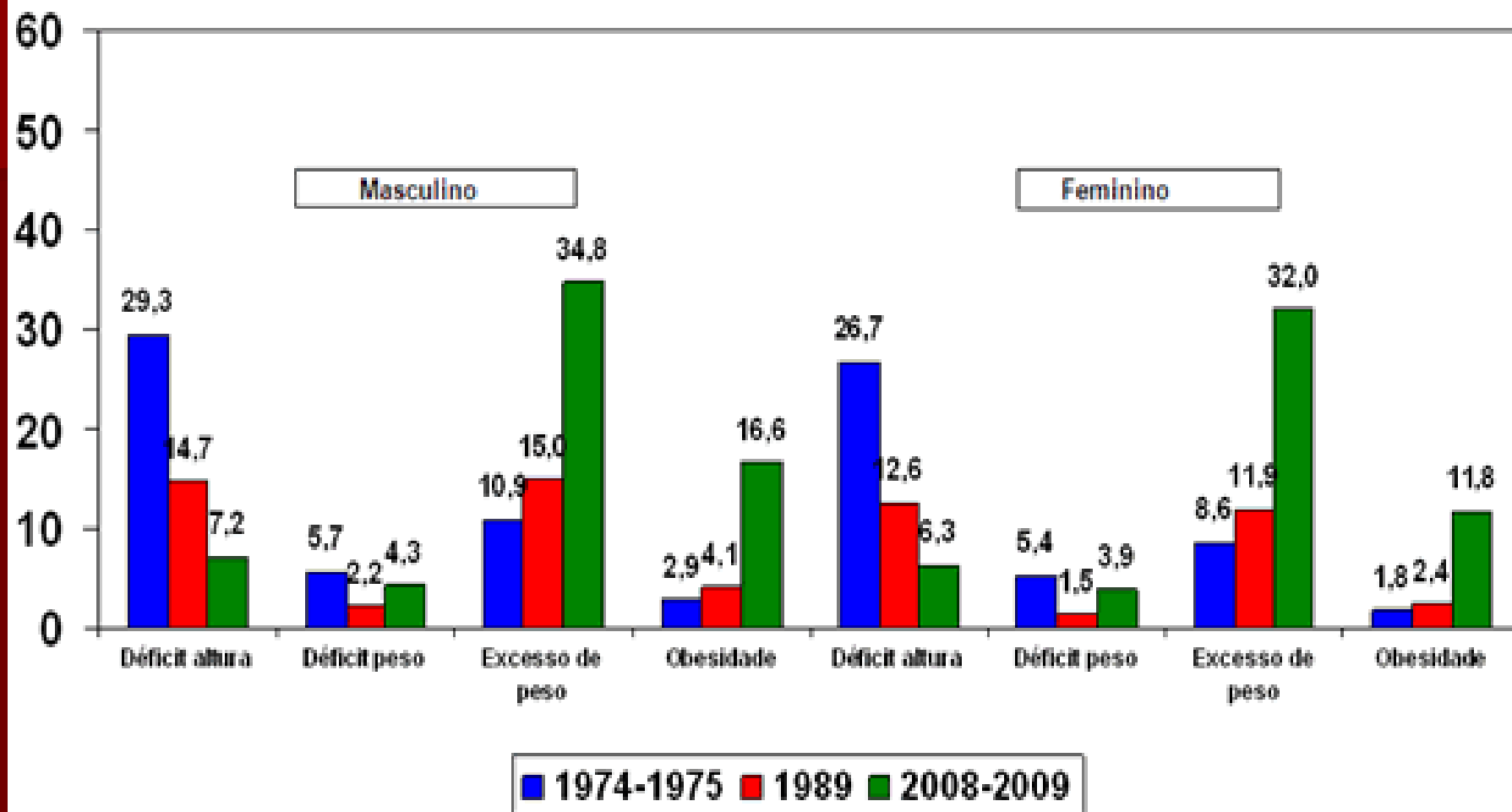
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Declaração de Conflitos de Interesses

**Resolução CFM nº 1595/2000, 18/05/2000
RDC ANVISA nº 102, 30/11/2000**

- ◆ **Nos últimos 5 anos, realizou palestras e consultorias para os seguintes laboratórios :**
- ◆ **MSD, Pfizer, Bayer, Novartis**
- ◆ **Sem vínculo público ou governamental**

Obesidade no Brasil



Fontes: IBGE, Estudo Nacional da Despesa Familiar 1974-1975; Instituto Nacional de Alimentação e Nutrição, Pesquisa Nacional sobre Saúde e Nutrição 1989; IBGE, Diretoria de Pesquisas, Coordenação de Trabalho e Rendimento, Pesquisa de Orçamentos Familiares 2008-2009

Consequências

- (WHO) 2,8 milhões de mortes/ano.
- Maior predisposição a infecções.

Fatores de risco e de mal prognóstico para infecção em obesos

■ Trato respiratório

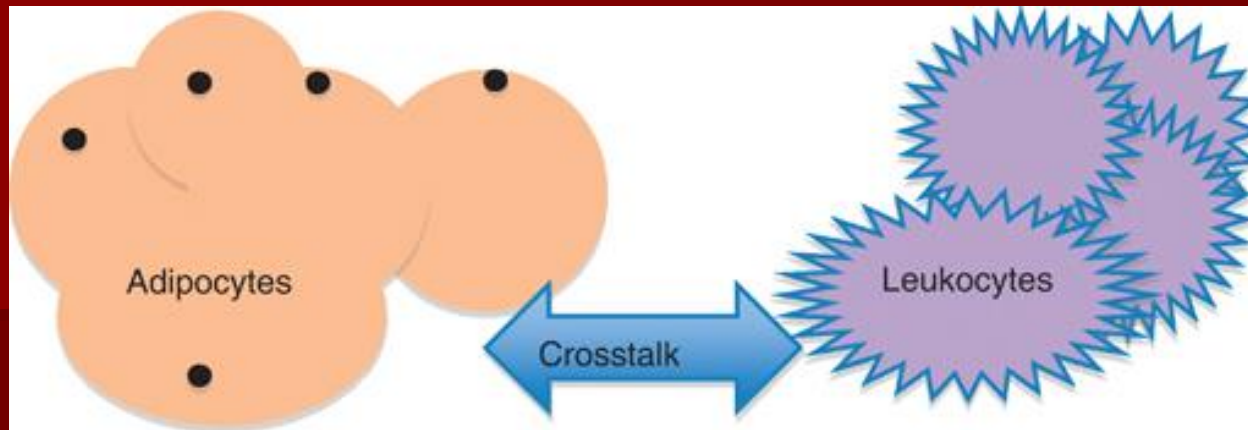
- Restrição pulmonar
- Diminuição do volume pulmonar
- Alteração de ventilação perfusão
- Apneia do sono obstrutiva
- Predisposição a embolia pulmonar
- Desregulação da resposta imune pulmonar

■ Pele partes moles e ossos

- Distúrbios da micro e macro circulação
- Diminuição da cicatrização
- Linfedema

■ Sistema imunológico

- Diminuição de quimiotaxia
- Alteração na diferenciação de macrófagos
- Desregulação da produção de citocinas
- Alteração da comunicação celular do Sistema imune e adipócitos



a

Altered secretion of

Leptin TNF-alpha MCP-1

Adiponectin IL-6

Resistin Visfatin

Omentin IFN-alpha/beta

b

Altered T-cell proliferation, Th1 response, lymphopoiesis, inflammatory response (dysregulation), macrophage differentiation

- CD8+ decreased and CD4+ cells decreased/increased
- Decreased natural killer cell activity
- Decreased antigen presentation of dendritic cells

Effect of Body Mass Index on the Outcome of Infections: A Systematic Review

A. P. ATHANASOULIA ¹, D. E. KARAGEORGOPOULOS ¹, G. PEPPAS ¹, M. E. FALAGAS^{1,2};

- **Background:** Both obesity and the underweight state have been thought to predispose to the acquisition of various types of infections. Whether the outcomes of infections differ by body weight category has not been adequately studied. **Methods:** Studies reporting data on the outcomes of patients with bacterial infections with regard to body weight category were identified through searching PubMed, the Cochrane Central Register of Controlled Trials and bibliographies of relevant articles. **Results:** Eleven studies (10 prospective cohort studies) were included in this review involving a total of 3339 patients. **Seven studies showed an association of patient outcomes (mortality in 6/7 studies) with body weight categories.** This was shown in multivariate analyses in 4 of the 5 studies that reported relevant data. **Obese or morbidly obese patients with infections had worse outcomes compared to all other body weight groups** combined or to normal weight patients, in 4 of the 7 studies that reported relevant data; findings were not significant in the remaining 3 studies. Patients with a low body mass index (BMI) had worse outcomes compared to all other BMI groups combined, in 3 of the 5 studies that reported relevant data; findings were not significant in the remaining 2 studies. Low BMI was associated with worse outcomes in patients with lower respiratory tract infections in 3 of the 4 relevant studies. **Conclusions:** Although not consistently reported, an association of both ends of the distribution of body weight with worse outcomes of patients with infections might exist, and merits further investigation.

Infecção do trato urinário

Pneumonias

Infecções de pele

Infecção do sítio cirúrgico

Sepse

Infecções em
cirurgia bariátrica



Terapia antimicrobiana apropriada

Antibioticoterapia apropriada

■ Empírica

“Antibiótico que cobre os agentes causais da infecção”

OBS: Farmacocineticamente adequada

■ Definitiva

“ Antibiótico que apresenta comprovada atividade frente ao patógeno significativo da infecção”

OBS: Farmacocineticamente adequada

PK/PD em obesos

- Maior porcentagem de tecido adiposo.
- Menor porcentagem de massa magra.
- Menor porcentagem de água.

Consequência em PK

- Débito cardíaco

- Função renal

- Função hepática

Clearance
Intervalo de doses

- Volume sanguíneo

- Volume de

distribuição (V_d)

Definir dose de ataque e
dose de manutenção

Classificação	Índice de massa corpórea (BMI)	% peso ideal (IBW)
Abaixo do peso	< 18.5 Kg/m ²	<80%
Peso normal	18.5 - 24.99 Kg/m ²	80-125 %
Sobrepeso	25 – 29.99 Kg/m ²	126-190%
Obesidade classe I	30 – 34.99 Kg/m ²	
Obesidade classe II	35 – 39.99 Kg/m ²	
Obesidade classe III	> 40 Kg/m ²	>190 %

BMI	Cálculo do peso ideal
$\frac{\text{Peso}}{\text{Altura (m)}^2}$	IBW (homens) = 50Kg + 2,3Kg x (polegadas (2,54 cm) acima de 5 pés (1.65 m)) IBW (mulher) = 45Kg + 2,3Kg x (polegadas (2,54 cm) acima de 5 pés (1.65 m))

Cálculo do clearance de creatinina estimado (Cockcroft e Gaut)

Método	Equação
Original	$(140 - \text{idade}) \times \text{peso total} / \text{creatinina sérica} \times 72$
Modificado	$(140 - \text{idade}) \times \text{peso ideal} / \text{creatinina sérica} \times 72$
Modificado com fator de correção	$(140 - \text{idade}) \times (\text{peso ideal} + 0,4 \times (\text{peso total} - \text{peso ideal})) / \text{creatinina sérica} \times 72$
<i>CLcr(homens)</i>	$(137 - \text{idade}) \times [(0.285 \times \text{peso total} + (12.1 \times \text{altura}^2))] / (51 \times \text{creatinina sérica})$
<i>CLcr(mulheres)</i>	$(146 - \text{idade}) \times [(0.287 \times \text{peso total}) + (9.74 \times \text{altura}^2)] / (60 \times \text{creatinina sérica})$

Estimativa do volume de distribuição (Vd)

$$Vd (\text{obeso}) = Vd (\text{não obeso}) \times \text{peso corporal ajustado}$$

$$\text{Peso corporal ajustado} = \text{IBW (peso ideal)} + (C (\text{fator de correção}) \times \text{Peso total} - \text{IBW})$$

Fator de correção (C)

0,4 – ATB hidrofílicos (0,37- 0,58)

0,3 - Beta lactâmicos

0,45 - quinolonas

Cálculo da meia vida

$$T_{1/2} = (0,693 \times V_d) / \text{clearance}$$

Tempo para Steady state	3-5 $T_{1/2}$ (meia vida)
Tempo para total eliminação da droga	5 $T_{1/2}$ (meia vida)

Table III: Literature-Based Antibacterial Dosing Recommendations for Obese Patients

Antibacterial Agent & Reference (*drug manufacturer)	Primary Considerations	Adult, non-obese, normal renal function		Recommendation(s) (for explanation see text and references cited)
		Vd (L/kg)	t _{1/2} (h)	
Aminoglycosides				
Amikacin ¹⁹	- Aminoglycosides are primarily distributed into extracellular fluids (ECF). - Higher CL, but greater Vd cancels out effect; alteration in dosage interval not necessary.	0.26	2	- Initial doses should be based on Vd using ABW with correction factor of 0.4 (ABW=IBW+0.4[TBW-IBW]). - Final dosage adjustments should be based on serum concentrations.
Gentamicin ^{11,13}		0.25	1.5-4	
Tobramycin ^{11,13}		0.26	1.6-3	
β-Lactams / Penicillins				
Ampicillin ²⁰	- Distributed in adipose tissue to some extent, but serum concentration not reported.	0.27-0.29	1-1.9	- No dose adjustment recommended.
Ampicillin-Sulbactam*	- No data available.	A: 0.27-0.29 S: 0.34	A: 1-1.9 S:1-1.3	- No information on obesity dosing available. Base dose on Vd using ABW with correction factor for H ₂ O composition of adipose tissue (ABW=IBW + 0.3 [TBW-IBW]). ²
Nafcillin ²¹	- Significant increase in Vd (almost double that of non-obese parameter). - CL unaffected.	0.57-1.55	0.5-1	- Increase non-obese dose of 2G IV q 4h to 3G IV q 6h in obese individuals.
Penicillin G ²²	- Drug absorption and serum levels not altered by obesity.	0.47	0.3-0.8	- No dose adjustment recommended.
Piperacillin-Tazobactam*	- Not evaluated in obese patients; multi-center trials studied patients with mean TBW of 73.3 kg. - CL and Vd not affected by chages in TBW.	0.14-0.23	0.9	- Base dose on diagnosis and CLcr.
Ticarcillin-Clavulanate*	- No data available.	T:0.15 C: 0.29	T: 1 C: 1-1.5	- Base dose on Clcr.
β-Lactams / Cephalosporins				
Cefazolin ^{23,24}	- In surgical prophylaxis, lower mean serum and adipose tissue concentrations in obese patients. - Higher prophylactic doses needed to achieve serum and tissue concentrations similar to those in non-obese patients.	0.13-0.22	1.5-2.5	- Use 2G for surgical prophylaxis. - Pories et al. suggest 1G IV, 2h before surgery and at induction of anesthesia, followed by 500mg IV q 6h x 8 doses.
Cefepime*	- Hydrophilic drug. - No data available.	0.2-0.29	2	- No information on obesity dosing available. Base dose on Vd using ABW with correction factor for H ₂ O composition of adipose tissue (ABW=IBW + 0.3 [TBW-IBW]). ²
Cefotaxime ²⁵	- Hydrophilic drug. Vd and CL increased 50% and 25%, respectively in patients ranging from 190% to 210% of IBW.	0.46-0.53	0.8-1.4	- Base dose on Vd using ABW with correction factor for H ₂ O composition of adipose tissue (ABW=IBW + 0.3 [TBW-IBW]). ²
Cefotetan*, ²⁶	- Clinical efficacy for prophylaxis in cesarean section patients weighing 106-305 pounds was 93%.	0.11-0.2	3-4.6	- No dose adjustment recommended.
Ceftazidime*	- No data available.	0.28-9.4	1.6-2	- Base dose on CLcr.
Ceftriaxone*	- No data available.	0.08-0.19	5.8-8.7	- No information on obesity dosing available. Base dose on Vd using ABW with correction factor for H ₂ O composition of adipose tissue (ABW=IBW + 0.3 [TBW-IBW]). ²
Cefuroxime*	- No data available.	0.17-0.31	1.1-1.9	- Base dose on CLcr.

Table III: Literature-Based Antibacterial Dosing Recommendations for Obese Patients (continued)

Antibacterial Agent & Reference (*drug manufacturer)	Primary Considerations	Adult, non-obese, normal renal function		Recommendation(s) (for explanation see text and references cited)
		Vd (L/kg)	t _{1/2} (h)	
β-Lactams / Carbapenems				
Ertapenem ^{27,28}	- AUC was significantly decreased in obese and morbidly obese patients; however, no dosing adjustment was recommended.	0.11	4	- Use standard dose of 1G/day.
Meropenem ²⁹	- Increased CL, Vd, and T _{1/2} . - Percentage of time the dose was above the MIC during an 8h dosing interval was not significantly different.	0.33-0.43	1	- No dose adjustment recommended.
Imipenem-Cilastatin*	- No data available.	0.14-0.33	1	- Base dose on CLcr.
Fluoroquinolones				
Ciprofloxacin ^{14,30}	- Less distributed to adipose tissue, Vd increased by 23%, increased CL, and lower C _{max} ; however, concentrations still within recommended therapeutic range.	1.2-2.7	3-6 (Extended-release: 6-7)	- Dose should be based on Vd using ABW with correction factor of 0.45 (ABW = IBW + 0.45[TBW-IBW]).
Levofloxacin*	- Drug is lipophilic, and widely distributed into body tissues.	1.25	6-8	- No information on obesity dosing available. - Base dose on CLcr.
Moxifloxacin*	- No data available.	1.7-2.7	14.8	- Use standard dose of 400mg IV/PO daily.
Macrolides				
Azithromycin*	- No data available.	23-31	11-68	- No information on obesity dosing available.
Erythromycin ³¹	- Peak concentrations similar in obese and non-obese adults.	0.57	1-1.5	- Base dose on IBW.
Miscellaneous				
Acyclovir ³²	- Pharmacokinetics not significantly different in obese and non-obese groups. - Half-life depends on renal function.	0.8	2.2-20	- Base dose on IBW.
Amphotericin B ³³	- Drug is lipophilic. - Zucker rats with hyperlipoproteinemia:↓Vd, ↓CL, ↑ renal toxicity.	4	360	- Use traditional dosing of 0.5-1.5mg/kg based on TBW.
Aztreonam*, ³⁴	- Drug is lipophilic.	0.1-0.2	1.5-3	- Use dose at upper end of range for treating serious infections in morbidly obese adults.
Clindamycin*	- No data available.	0.6-1.2	1.5-5	- No information on obesity dosing available.
Dalfopristin-Quinupristin*	- Terminal phase Vd was similar between obese and non-obese subjects. - Distributes more into lean body mass than into fat tissue.	D: 0.24 Q: 0.45 (dose-dependent)	1.3-1.5	- Use traditional q 8h or q 12h dosing of 7.5mg/kg based on TBW.
Daptomycin ³⁵	- Increased Vd and CL in obese vs. non-obese subjects. - Large molecular mass with high polarity, low lipid solubility, and high plasma protein binding. - Exposure increased by 25-30% when dose based on TBW, but still safe and tolerated in subjects ranging from 56-147kg.	0.12	7-11	- Base dose on TBW.
Doxycycline*	- Drug is lipophilic.	0.75	15-24	- No information on obesity dosing available.
Fluconazole ³⁶	- Hydrophilic agent, eliminated by kidney.	0.56-0.82	30	- A higher dose is recommended (e.g., 1200mg/day for candida fungaemia in necrotizing fasciitis).
Linezolid ³⁷	- Prolonged inhibitory activity observed despite ↓serum concentrations.	0.57-0.86	5	- Use standard dose of 600mg IV/PO q 12h.
Metronidazole*	- No data available.	0.25-0.85	6-14	- No information on obesity dosing available.
Sulfamethoxazole-Trimethoprim*	- No data available.	S: 0.360 T: 2	S: 8-11 T: 6-17	- No information on obesity dosing available.
Tigecycline*	- Study subjects weighed 39-200kg.	7-9	42	- Use traditional dose of 100mg IV followed by 50mg IV q 12h.
Vancomycin ³⁸⁻⁴⁰	- Increased Vd and CL in obese patients correlates better with TBW.	0.7	7-9	- Base dose on TBW, giving 20-30mg/kg/day. - If necessary, shorten administration interval to maintain serum trough >5mg/L.

Cenários Farmacocinéticos em infecções

**Aumento do
Débito
cardíaco**



**Aumento do
clearance**

**↑da
permeabilidade
capilar & ou
alteração da
ligação protéica**



**Aumento do
volume de
distribuição**



**Baixa concentração
Plasmática**

**Funções
orgânicas
preservada**



**Volume de
Distribuição
inalterado**



**Concentração
Plasmática
Normal**

**Disfunção
orgânica
Múltiplas
(renal/hepática)**



**Diminuição do
clearance do ATB**



**Concentração
Plasmática
elevada**

**ANTIBIÓTICOS
HIDROFÍLICOS**

PK habitual

VOLUME DE DISTRIBUIÇÃO
BAIXO
CLEARANCE PREDOMINANTE
RENAL
BAIXA PENETRAÇÃO
INTRACELULAR

**ANTIBIÓTICOS
LIPOFÍLICOS**

VOLUME DE DISTRIBUIÇÃO
ALTO
CLEARANCE PREDOMINANTE
HEPÁTICO
ALTA PENETRAÇÃO
INTRACELULAR

**PK alterada
em pacientes
de críticos**

↑ VOLUME DE DISTRIBUIÇÃO
CLEARANCE ↑ OU ↓
DEPENDENDO DA FUNÇÃO
RENAL

VOLUME DE DISTRIBUIÇÃO
INALTERADO
CLEARANCE ↑ OU ↓
DEPENDENDO DA FUNÇÃO
HEPÁTICA

Exemplos

B –LACTÂMICOS
AMINOGLICOSÍDEOS
GLICOPEPTÍDEOS
LINEZOLIDA
COLISTINA
FOSFOMICINA

FLUOROQUINOLONAS
MACROLÍDEOS
LINCOSAMINAS
SULFAS
TIGECICLINA /TETRA
TUBERCULOSTATICOS

Adjustment of dosing of antimicrobial agents for bodyweight in adults

Matthew E Falagas, Drosos E Karageorgopoulos

www.thelancet.com Published online October 28, 2009 DOI:10.1016/S0140-6736(09)60743-1

- Adequação de doses :
- Beta lactâmicos : 30% acima
- Aminoglicosídeos : dose massa magra + 40% da dose do excesso de peso
- Quinolonas : – doses máximas
- Vancomicina : monitorar concentração sérica.

Legacy Health – Modified from original work by Lindsie M. Froehlich

ADULT WEIGHT-BASED ANTIMICROBIAL DOSAGE ADJUSTMENT TABLE CrCr

	WEIGHT (kg)	CrCl > 50	CrCl 30 – 50	CrCl 10 – 30	CrCl <10
PENICILLINS					
<u>Ampicillina</u>	<80	1gm q6h ^b	1gm q8	1gm q12h	1gm q24h
	80-139	2gm q6h ^a	2gm q8h	2gm q12h	2gm q24h
	⚡ 140	3gm q6h ^a	3gm q8h	3gm q12h	3gm q24h
<u>Oxacilina</u>	< 100	2gm q4h	No dosage adjustment necessary		
	⚡ 100	3gm q4h			
<u>Penicilina G</u>	< 100	3mU q4h	2mU q4h	2mU q8h	1mU q8h
	⚡ 100	4mU q4h	3mU q4h	3mU q8h	2mU q8h
<u>Ampicilina/ sulbactam</u>	< 80	1.5gm q6h	1.5gm q8h	1.5gm q12h	1.5gm q24h
	80 – 139	3gm q6h	3gm q8h	3gm q12h	3gm q24h
	⚡ 140	4.5gm q6h	4.5gm q8h	4.5gm q12h	4.5gm q24h
<u>Piperacilina/ tazobactam</u>		CrCl >40	CrCl 20 – 40	CrCl <20	
	< 100 PSE	3.375gm q6	2.25gm q6h*	2.25gm q8h*	
		4.5gm q6h	3.375gm q6h*	2.25gm q6h*	
	100 - 139 PSE	3.375gm q4h	2.25gm q4h*	2.25gm q6h*	
		4.5gm q4h	3.375gm q4h*	2.25gm q4h*	
	⚡ 140 PSE	4.5gm q6h	3.375gm q6h*	2.25gm q6h*	
		6gm q6h	4.5gm q8h*	3.375gm q8h*	

CEPHALOSPORINS

	WEIGHT (kg)	CrCl > 50	CrCl 30 – 50	CrCl 10 – 30	CrCl <10
<u>Cefazolina</u>	< 80	1gm q8h		500mg q12h*	500mg q24h*
	80 – 149	2gm q8h		1gm q12h*	1gm q24h*
	◆ 150	3gm q8h		2gm q12h*	2gm q24h*
<u>Ceftazidima</u>	< 80	1gm q8h	1gm q12h	1gm q24h	500mg q24h*
	80 – 149	2gm q8h	2gm q12h	2gm q24h	1gm q24h*
	◆ 150	3gm q8h	3gm q12h	3gm q24h	1gm q24h*
<u>Ceftriaxona</u>	< 80	1gm q24h	No dosage adjustment necessary		
	80 - 129	2gm q24h			
	◆ 130	3gm q24h			
<u>Cefotetan</u>	< 80	1gm q12h	Same dose	1gm IV q24h	1gm q48h
	81 – 139	2gm q12h	Same dose	2gm q24h	2gm q48h
	◆ 140	3gm q12h	Same dose	3gm q24h	3gm q48h
<u>Cefepime</u>	< 100	1gm q8h	1gm q12h	1gm q24h	500mg q24h*
	◆ 100	2gm q8h	2gm q12h	2gm q24h	1gm q24h*

CARBAPENEMS

	WEIGHT (kg)	CrCl > 50	CrCl 30 – 50	CrCl 10 – 30	CrCl <10	CrCl > 50
<u>Ertapenem</u>	< 100	1gm q24h	Same dose		500mg q24h*	Same dose*
	💎 100	2gm q24h	Same dose		1gm q24h*	500mg q24h*
<u>Meropenem</u>	< 100	1gm q8h	1gm q12h		500mg q12h*	500mg q24h*
	💎 100	2gm q8h	2gm q12h		1gm q12h*	1gm q24h*

FLUOROQUINOLONES

<u>Ciprofloxacin</u>	< 100	400mg q12h			400mg q24h	200mg q24h*
	101 - 139	600mg q12h			600mg q24h	300mg q24h*
	💎 140	800mg q12h			800mg q24h	400mg q24h*
<u>Moxifloxacin</u>	< 100	400mg q24h	No dosage adjustment necessary			
	101 – 139	600mg q24h				
	💎 140	800mg q24h				
	💎 150	750mg q24h				
	WEIGHT (kg)	CrCl > 50	CrCl 30 – 50		CrCl 10 – 30	CrCl <10

MISCELLANEOUS

<u>Aztreonam</u>	< 80	1gm q6h	500mg q6h*	250mg q6h*
	❖ 80	2gm q6h	1gm q6h*	500mg q6h*
<u>Clindamicina</u>	< 80	600mg q8h	No dosage adjustment necessary	
	❖ 80	900mg q8h		
<u>Daptomicina</u>	Use TBW	4-6 mg/kg q24h		q48h
<u>Fluconazol</u>	<80	400mg q24h	200mg q24h*	
	80 - 149	800mg q24h	400mg q24h*	
	❖ 150	1200mg q24h	600mg q24h*	
<u>Linezolid</u>	< 150	600mg q12h	No dosage adjustment necessary	
	❖ 150	600mg q8h		

*Give loading dose as if normal renal function x 1, then decrease dose per protocol ^aUse same dose q4h for endocarditis and meningitis ^bUse 2 gm q4h for endocarditis and meningitis PSE = Pseudomonas infection (excluding urinary tract infection TBW: Total body weight (kg)

Conclusões

- A utilização “apropriada” de antibióticos em paciente obesos requer esforço intenso do médico e ou do farmacêutico clínico afim de obter a melhor performance terapêutica e menor toxicidade.
- Difundir os conceitos de PK/PD entre as equipes médicas é importante para melhora o padrão de prescrição nesta população.

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Obrigado !!!