Supplementary tables

Table S1: Empirical antimicrobial therapy of abdominal VGEI without a fistula

Setting	Antimicrobial therapy[2]	Dosage
Community-acquired[1]	Amoxicillin/clavulanic acid[3]	2.2 g i.v. q6h
	plus/minus	
	Vancomycin[4]	Loading dose 30 mg/kg, followed by 15 mg/kg q12h[2]
	or	
	Daptomycin[4]	10-12 mg/kg body weight i.v. q24h
	Ceftriaxone[5]	2 g i.v. q24h
	plus	
	Metronidazole	500 mg p.o. q8h
	plus	
	Vancomycin[4]	Loading dose 30 mg/kg, followed by 15 mg/kg q12h[2]
	or	
	Daptomycin[4]	10-12 mg/kg body weight i.v. q24h
Hospital-acquired[1]	Piperacillin/tazobactam	4.5 g i.v. q6h
	plus/minus	
	Vancomycin[4]	Loading dose 30 mg/kg, followed by 15 mg/kg q12h[2]
	or	
	Daptomycin[4]	10-12 mg/kg body weight i.v. q24h
	Cefepime[5]	2 g i.v. q8h
	plus	
	Metronidazole	500 mg p.o. q8h
	plus	
	Vancomycin[4]	Loading dose 30 mg/kg, followed by 15 mg/kg q12h[2]
	or	
	Daptomycin[4]	10-12 mg/kg body weight i.v. q24h
	Meropenem[5,6]	2 g i.v. q8h
	plus	
	Vancomycin[4]	Loading dose 30 mg/kg, followed by 15 mg/kg q12h[2]
	or	
	Daptomycin[4]	10-12 mg/kg bodyweight i.v. q24h

Notes

[1] Definitions:

Healthcare associated VGEI: 1) onset of VGEI >48h after hospital admission or within 3 months after discharge from hospitalization (duration two days or more); 2) onset of VGEI within 3 months after a significant procedure known to be associated with bacteremia and an increased risk of VGEI and performed during hospitalization or ambulatory setting; 3) onset of VGEI within one month of extensive out-of-hospital contact with healthcare defined as receipt of intravenous treatment, wound care, or vascular manipulations; 4) residence in a nursing home or similar facility

Community acquired VGEI: does not meet criteria for healthcare associated VGEI

[2] All antibiotics need to be adjusted for renal function. Consider therapeutic drug monitoring. Adjust dosing strategy based on individual factors such as body weight. Consider also extended or continuous infusions of beta-lactams in critically-ill patients

[3] Amoxicillin/clavulanic acid may be replaced by ampicillin/sulbactam (3 g i.v. q6h)

[4] In case of high prevalence of MRSA or MRSE. Consider daptomycin as the first option in the presence of renal insufficiency or concomitant nephrotoxic treatment. In obese patients daptomycin dosage should be based on adjusted body weight. A possible alternative for vancomycin or daptomycin is teicoplanin 12 mg/kg body weight i.v. 0, 12, 24h (loading dose), and thereafter 12 mg/kg body weight q24h alternatively

[5] In case of cephalosporin-containing regimen or use of carbapenem, a glycopeptide should be added to provide coverage against enterococci

[6] In case of high prevalence of MDR-GNB. In the presence of local high resistance rates to meropenem, consider alternative options such as novel cephalosporins, like ceftazidime-avibactam or ceftolozane-tazobactam (plus metronidazole).

Table S2: Empirical antimicrobial therapy of thoracic VGEI without an aorto-esophageal fistula

Setting	Antimicrobial therapy[2]	Dosage
Community-acquired[1]	Flucloxacillin **plus** Vancomycin[3] **or** Daptomycin[3]	2 g i.v. q4h Loading dose 30 mg/kg, followed by 15 mg/kg q12h[2] 10-12 mg/kg body weight i.v. q24h
	Cefazolin **plus** Vancomycin[3] **or** Daptomycin[3]	2 g i.v. q8h Loading dose 30 mg/kg, followed by 15 mg/kg q12h[2] 10-12 mg/kg body weight i.v. q24h
	Amoxicillin/clavulanic acid[4] **plus/minus** Vancomycin[3] **or** Daptomycin[3]	2.2 g i.v. q6h Loading dose 30 mg/kg, followed by 15 mg/kg q12h[2] 10-12 mg/kg body weight i.v. q24h
Hospital-acquired[1]	Piperacillin/tazobactam[6] **plus/minus** Vancomycin[3] **or** Daptomycin[3]	4.5 g. i.v. q6h Loading dose 30 mg/kg, followed by 15 mg/kg q12h[2] 10-12 mg/kg body weight i.v. q24h

Notes

[1] Definitions:

Healthcare associated VGEI: 1) onset of VGEI >48h after hospital admission or within 3 months after discharge from hospitalization (duration two days or more); 2) onset of VGEI within 3 months after a significant procedure known to be associated with bacteremia and an increased risk of VGEI and performed during hospitalization or ambulatory setting; 3) onset of VGEI within one month of extensive out-of-hospital contact with healthcare defined as receipt of intravenous treatment, wound care, or vascular manipulations; 4) residence in a nursing home or similar facility

Community acquired VGEI: does not meet criteria for healthcare associated VGEI

[2] All antibiotics need to be adjusted for renal function. Consider therapeutic drug monitoring. Adjust dosing strategy based on individual factors such as body weight. Consider also extended or continuous infusions of beta-lactams in critically-ill patients

[3] In case of high prevalence of MRSA or MRSE. Consider daptomycin as the first option in the presence of renal insufficiency or concomitant nephrotoxic treatment. In obese patients daptomycin dosage should be based on adjusted body weight. A possible alternative for vancomycin or daptomycin is teicoplanin 12 mg/kg body weight i.v. 0, 12, 24h (loading dose), and thereafter 12 mg/kg body weight q24h alternatively

[4] Amoxicillin/clavulanic acid may be replaced by ampicillin/sulbactam (3 g i.v. q6h)

[5] In case of cephalosporin-containing regimen or use of carbapenem, a glycopeptide should be added to provide coverage against enterococci

[6] In the presence of local high resistance rates consider alternative options such as carbapenems or novel cephalosporins like ceftazidime-avibactam or ceftolozane-tazobactam (plus metronidazole)

Table S3: Empirical antimicrobial therapy of abdominal VGEI <u>with</u> an aorto-enteric fistula or thoracic VGEI <u>with</u> an aorto-esophageal fistula

Setting	Antimicrobial therapy[2]	Dosage
Community-acquired[1]	Amoxicillin/clavulanic acid[3] **plus/minus** Vancomycin[4] **or** Daptomycin[4] **plus/minus** Caspofungin[5,6]	2.2 g i.v. q6h Loading dose 30 mg/kg, followed by 15 mg/kg q12h[2] 10-12 mg/kg body weight i.v. q24h Loading dose 70 mg i.v (day 1), followed by 50 mg i.v. q24h
	Ceftriaxone **plus** Metronidazole **plus** Vancomycin[4,7] **or** Daptomycin[4] **plus/minus** Caspofungin[5,6]	2 g i.v. q24h 500 mg p.o. q8h Loading dose 30 mg/kg, followed by 15 mg/kg q12h[2] 10-12 mg/kg body weight i.v. q24h Loading dose 70 mg i.v (day 1), followed by 50 mg i.v. q24h
Hospital-acquired[1]	Piperacillin/tazobactam **plus/minus** Vancomycin[4] **or** Daptomycin[4] **plus/minus** Caspofungin[5,6]	4.5 g. i.v. q6h Loading dose 30 mg/kg, followed by 15 mg/kg q12h[2] 10-12 mg/kg body weight i.v. q24h Loading dose 70 mg i.v (day 1), followed by 50 mg i.v. q24h
	Cefepime **plus** Metronidazole **plus**	2 g i.v. q8h 500 mg p.o. q8h

	Vancomycin[4,7] **or** Daptomycin[4] **plus/minus** Caspofungin[5,6]	Loading dose 30 mg/kg, followed by 15 mg/kg q12h[2] 10-12 mg/kg body weight i.v. q24h Loading dose 70 mg i.v (day 1), followed by 50 mg i.v. q24h
	Meropenem[8] **plus** Vancomycin[4,7] **or** Daptomycin[4] **plus/minus** Caspofungin[5,6]	2 g i.v. q8h Loading dose 30 mg/kg, followed by 15 mg/kg q12h[2] 10-12 mg/kg body weight i.v. q24h Loading dose 70 mg i.v (day 1), followed by 50 mg i.v. q24h

Notes

[1] Definitions:

Healthcare associated VGEI: 1) onset of VGEI >48h after hospital admission or within 3 months after discharge from hospitalization (duration two days or more); 2) onset of VGEI within 3 months after a significant procedure known to be associated with bacteremia and an increased risk of VGEI and performed during hospitalization or ambulatory setting; 3) onset of VGEI within one month of extensive out-of-hospital contact with healthcare defined as receipt of intravenous treatment, wound care, or vascular manipulations; 4) residence in a nursing home or similar facility

Community acquired VGEI: does not meet criteria for healthcare associated VGEI

[2] All antibiotics need to be adjusted for renal function. Consider therapeutic drug monitoring. Adjust dosing strategy based on individual factors such as body weight. Consider also extended or continuous infusions of beta-lactams in critically-ill patients

[3] Amoxicillin/clavulanic acid may be replaced by ampicillin/sulbactam (3 g i.v. q6h)

[4] In case of high prevalence of MRSA or MRSE. Consider daptomycin as the first option in the presence of renal insufficiency or concomitant nephrotoxic treatment. In obese patients daptomycin dosage should be based on adjusted body weight. A possible alternative for vancomycin or daptomycin is teicoplanin 12 mg/kg body weight i.v. 0, 12, 24h (loading dose), and thereafter 12 mg/kg body weight q24h alternatively

[5] In case of risk factors like: antibiotic therapy preceding the infection, ICU patients, sepsis, high candida score, parenteral nutrition, multifocal fungal colonization

[6] Alternative regimens: anidulafungin, loading dose 200 mg i.v. q24h (day 1), followed by 100 mg i.v.

q24h **or** micafungin 100 mg i.v. q24h

[7] In case of cephalosporin-containing regimen or use of carbapenem, a glycopeptide should be added to provide coverage against enterococci

[8] In case of high prevalence of MDR-GNB. In the presence of local high resistance rates to meropenem, consider alternative options such as novel cephalosporins, like ceftazidime-avibactam or ceftolozane-tazobactam (plus metronidazole).

Table S4: Empirical antimicrobial therapy of extracavitary VGEI

Setting	Antimicrobial therapy[2]	Dosage
Community-acquired[1]	Amoxicillin/clavulanic acid[3]	2.2 g i.v q6h
	plus/minus	
	Vancomycin[4]	Loading dose 30 mg/kg, followed by 15 mg/kg q12h[2]
	or	
	Daptomycin[4]	10-12 mg/kg body weight i.v. q24h
	Ceftriaxone	2 g i.v. q24h
	plus/minus	
	Vancomycin[4,5]	Loading dose 30 mg/kg, followed by 15 mg/kg q12h[2]
	or	
	Daptomycin[4]	10-12 mg/kg body weight i.v. q24h
Hospital-acquired[1]	Piperacillin/tazobactam	4.5 g. i.v. q6h
	plus/minus	
	Vancomycin[4]	Loading dose 30 mg/kg, followed by 15 mg/kg q12h[2]
	or	
	Daptomycin[4]	10-12 mg/kg body weight i.v. q24h
	Cefepime	2.2 g i.v. q8h
	plus/minus	
	Vancomycin[4,5]	Loading dose 30 mg/kg, followed by 15 mg/kg q12h[2]
	or	
	Daptomycin[4]	10-12 mg/kg body weight i.v. q24h

Notes

[1] Definitions:

Healthcare associated VGEI: 1) onset of VGEI >48h after hospital admission or within 3 months after discharge from hospitalization (duration two days or more); 2) onset of VGEI within 3 months after a significant procedure known to be associated with bacteremia and an increased risk of VGEI and performed during hospitalization or ambulatory setting; 3) onset of VGEI within one month of extensive out-of-hospital contact with healthcare defined as receipt of intravenous treatment, wound care, or vascular manipulations; 4) residence in a nursing home or similar facility

Community acquired VGEI: does not meet criteria for healthcare associated VGEI

[2] All antibiotics need to be adjusted for renal function. Consider therapeutic drug monitoring. Adjust dosing strategy based on individual factors such as body weight. Consider also extended or continuous infusions of beta-lactams in critically-ill patients

[3] Amoxicillin/clavulanic acid may be replaced by ampicillin/sulbactam (3 g i.v. q6h)

[4] In case of high prevalence of MRSA or MRSE. Consider daptomycin as the first option in the presence of renal insufficiency or concomitant nephrotoxic treatment. In obese patients daptomycin dosage should be based on adjusted body weight. A possible alternative for vancomycin or daptomycin is teicoplanin 12 mg/kg body weight i.v. 0, 12, 24h (loading dose), and thereafter 12 mg/kg body weight q24h alternatively

[5] In case of cephalosporin-containing regimen and a graft located in the groin, a glycopeptide should be added to provide coverage against enterococci

Table S5: Treatment of staphylococcal VGEI

Pathogen	First-line treatment[1]	Alternative drugs, penicillin-allergic[1]
MSSA/MSSE	*Parenteral therapy* Flucloxacillin 2 g i.v. q4h **plus** Rifampicin 900-1200 mg divided in two to three doses p.o. [2] *Sequential therapy[3]* Levofloxacin 500 mg p.o. q12h[2] **plus** Rifampicin 900-1200 mg divided in two to three doses p.o.[2]	*Parenteral therapy* Cefazolin 2 g. i.v. q8h **plus** Rifampicin 900-1200 mg divided in two to three doses p.o.[2] *Sequential therapy[3]* Levofloxacin 500 mg p.o. q12h[2] **plus** Rifampicin 900-1200 mg divided in two to three doses p.o.[2]
MRSA/MRSE	*Parenteral therapy* Vancomycin 30 mg/kg, followed by 15 mg/kg bodyweight q12h[1] **plus** Rifampicin 900-1200 mg divided in two to three doses p.o.[2] *Sequential therapy[3]* Levofloxacin 500 mg p.o. q12h[4] **plus** Rifampicin 900-1200 mg divided in two to three doses p.o.[2]	*Parenteral therapy[5]* Daptomycin 10-12 mg/kg body weight i.v. q24h **plus** Rifampicin 900-1200 mg divided in two to three doses p.o.[2] *Sequential therapy[3]* Levofloxacin 500 mg p.o. q12h[2] **plus** Rifampicin 900-1200 mg divided in two to three doses p.o.[2]

Notes

[1] All antibiotics need to be adjusted for renal function. Consider therapeutic drug monitoring. Adjust dosing strategy based on individual factors such as body weight. Consider also extended or continuous infusions of beta-lactams in critically-ill patients

[2] Add rifampicin delayed e.g. after debridement and negative blood cultures.

[3] Sequential treatments: could be oral or long-acting (dalbavancin/oritavancin).

[4] Oral alternatives: clindamycin 600 mg q8h, cotrimoxazole 1 DS q8h, linezolid 600mg q12h, doxycycline 100 mg q12h or moxifloxacin 400 mg p.o. q24h. Due to the increased risk of aneurysms and dissection during fluoroquinolones treatment, a risk-benefit assessment should be performed

also considering the availability of alternative options.

[5] For MRSA/MRSE: alternative drugs: daptomycin plus ceftaroline or daptomycin and fosfomycin.

Table S6: Treatment of enterococcal VGEI

Pathogen	First-line treatment[1]	Alternative drugs, penicillin-allergic[1]
Enterococcus spp	*Parenteral therapy* Amoxicillin[2] 2 g i.v. q4h **plus** Ceftriaxone 2 g i.v. q12h **or** Amoxicillin[2] 2 g i.v. q4h **plus** Gentamicin 3 mg/kg body weight i.v. q24h *Sequential therapy[3]* Amoxicillin[2] 1 g p.o. q6h	*Parenteral therapy* Vancomycin 30 mg/kg, followed by 15 mg/kg body weight i.v. q12h[1] **or** Daptomycin 10-12 mg/kg body weight i.v. q24h **or** Teicoplanin 12 mg/kg body weight i.v. 0, 12, 24h (loading dose), and thereafter 12 mg/kg body weight i.v. q24h *Sequential therapy[3]* Doxycycline 100 mg p.o. q12h **or** Moxifloxacin 400 mg p.o. q24h[4] **or** Linezolid 600 mg p.o. q12h[5]

Notes

[1] All antibiotics need to be adjusted for renal function. Consider therapeutic drug monitoring. Adjust dosing strategy based on individual factors such as body weight. Consider also extended or continuous infusions of beta-lactams in critically-ill patients

[2] Alternative: ampicillin

[3] Sequential treatments: could be oral or long-acting (dalbavancin/oritavancin)

[4] Due to the increased risk of aneurysms and dissection during fluoroquinolones treatment, a risk-benefit assessment should be performed also considering the availability of alternative options

[5] Therapeutic drug monitoring because of myelotoxicity. Monitor lactate, differential blood count, polyneuropathy

Table S7: Treatment of streptococcal VGEI

Pathogen	First-line treatment[1]	Alternative drugs, penicillin-allergic[1]
Streptococcus spp, MIC of Penicillin ≤ 0.25	*Parenteral therapy* Penicillin G 4 Mio E i.v. q4h **or** Ceftriaxone 2 g i.v. q24h *Sequential therapy*[3] Amoxicillin[2] 1 g p.o. q6h	*Parenteral therapy* Vancomycin 30 mg/kg body weight, followed by 15 mg/kg bodyweight q12h[1] *Sequential therapy*[3,4] Doxycycline 100 mg p.o. q12h **or** Clindamycin 600 mg p.o. q8h
Streptococcus spp, MIC of Penicillin > 0.25	*Parenteral therapy* Penicillin G 4 Mio E i.v. q4h **plus** Gentamicin 3 mg/kg body weight i.v. q24h **or** Ceftriaxone 2 g i.v. q12h **plus** Gentamicin 3 mg/kg body weight i.v. q24h *Sequential therapy*[3] Clindamycin 600 mg p.o. q8h **or** Linezolid 600 mg p.o. q12h	*Parenteral therapy*[5] Vancomycin 30 mg/kg body weight, followed by 15 mg/kg bodyweight q12h[1] **plus** Gentamicin 3 mg/kg body weight i.v. q24h *Sequential therapy*[3] Clindamycin 600 mg p.o. q8h **or** Linezolid 600 mg p.o. q12h

Notes

[1] All antibiotics need to be adjusted for renal function. Consider therapeutic drug monitoring. Adjust dosing strategy based on individual factors such as body weight. Consider also extended or continuous infusions of beta-lactams in critically-ill patients

[2] Alternative: ampicillin

[3] Sequential treatments: could be oral or long-acting (dalbavancin/oritavancin).

[4] Other alternatives: oral cefadroxil or cephalexin.

[5] Daptomycin is not an effective drug for streptococci given the high-risk of resistance development

Table S8: Treatment of VGEI due to *Enterobacterales*

Pathogen	First-line treatment[1]	Alternative drugs[1]
Enterobacterales	*Parenteral therapy* Ceftriaxone 2 g i.v. q24h **or** Cefepime[2] 2 g i.v. q8h *Sequential therapy* Cotrimoxazole 1 DS p.o. q8h	*Parenteral therapy[3]* Ertapenem 1 g i.v. q24h **or** Meropenem 1 g i.v. q8h *Sequential therapy* Ciprofloxacin 500-750 mg p.o. q12h[4] **or** Levofloxacin 500 mg p.o. q12h[4]

Notes:

[1] All antibiotics need to be adjusted for renal function. Consider therapeutic drug monitoring. Adjust dosing strategy based on individual factors such as body weight. Consider also extended or continuous infusions of beta-lactams in critically-ill patients

[2] In case of AmpC producing pathogens

[3] Depending on pathogen susceptibility

[4] Due to the increased risk of aneurysms and dissection during fluoroquinolones treatment, a risk-benefit assessment should be performed also considering the availability of alternative options.

Table S9: Pathogen specific treatment of VGEI due to *P. aeruginosa*:

Pathogen	First-line treatment[1]	Alternative drugs[1]
P. aeruginosa	*Parenteral therapy* Ceftazidime 2 g i.v. q8h **or** Piperacillin/Tazobactam 4.5 g i.v. q6h *Sequential therapy* Ciprofloxacin 750 mg p.o. q12h[2]	*Parenteral therapy* Cefepime 2 g i.v. q8h **or** Meropenem 2 g i.v. q8h *Sequential therapy* Ciprofloxacin 750 mg p.o. q12h[2]

Notes:

[1] All antibiotics need to be adjusted for renal function. Consider therapeutic drug monitoring. Adjust dosing strategy based on individual factors such as body weight. Consider also extended or continuous infusions of beta-lactams in critically-ill patients

[2] Due to the increased risk of aneurysms and dissection during fluoroquinolones treatment, a risk-benefit assessment should be performed also considering the availability of alternative options.

Table S10: Suggested regimens for long-term suppressive antimicrobial therapy (SAT) for VGEI

Pathogen	**Suppressive antimicrobial therapy**	**Dosage**	**Common side effects[1]**
S. aureus[2,3] CoNS	Doxycycline[4] **or** Minocycline **or** Cotrimoxazole **or** Clindamycin	100 mg p.o. q12h 100 mg p.o. q12h 1 DS p.o. q8-12h 300 mg p.o. q8h	Photosensitivity, nausea, vomiting Hyperpigmentation Acute kidney injury, hyperkalemia Gastrointestinal disturbance, *C. difficile* infection, nausea
E. faecalis	Amoxicillin[4]	1 g p.o. q12h	Gastrointestinal disturbance
E. faecium[3]	Doxycycline[4] **or** Minocycline	100 g p.o. q12h 100 g p.o. q12h	Photosensitivity, nausea, vomiting Hyperpigmentation
Streptococcus spp	Amoxicillin[4] **or** Clindamycin **or** Doxycycline[4] **or** Minocycline	1 g p.o. q12h 300 mg p.o. q8h 100mg p.o. q12h 100mg p.o. q12h	Gastrointestinal disturbance Gastrointestinal disturbance, *C. difficile* infection, nausea Photosensitivity, nausea, vomiting Hyperpigmentation
Gram-negative bacilli	Co-trimoxazole **or** Ciprofloxacin (or Levofloxacin)	1 DS p.o. q12h 250 mg q12h	Acute kidney injury, hyperkalemia Risks of tendinopathy, QT prolongation and aortic aneurysm or dissection
No identification	Doxycycline[4] **or** Cotrimoxazole **or** Minocycline	100 mg p.o. q12h 1 DS p.o. q12h 100 mg p.o. q12h	Photosensitivity, nausea, vomiting Acute kidney injury, hyperkalemia Hyperpigmentation

Notes: DS, double strength;

[1] General side effects include allergies, intolerance, drug-associated fever

[2] Cephalexin or cefadroxil may be considered in case of MSSA

[3] Consider using dalbavancin or oritavancin as SAT in the context of *S. aureus* or *E. faecium* VGEI

[4] Consider lower dose of doxycycline 100mg q24h or amoxicillin 500mg q8h in case of favorable clinical course