Bactériémie en réanimation

C. Dupuis

Service de Médecine Intensive et Réanimation

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Épidémiologie

- Incidence – sources – microbiologie – résistances – mortalité - COVID

Diagnostic et bilan d'extension

- Modalité de réalisation des hémocultures
- Interprétation (bactériémie vrai versus contamination)
- Les nouveaux outils
- Bilan d'extension

Les modalités thérapeutiques d'une bactériémie

- Contrôle de la source
- Antibiothérapie probabiliste
- Bi antibiothérapie
- Monitorage
- Désescalation
- Durée

Quelques définitions

- **Bactériémie primitive** si pas de porte d'entrée
- **Bactériémie persistante:** si hémocultures toujours positives après trois jours d'antibiothérapie bien conduite
- **BSI: Bloodstream infection:** bactériémie
- **Community-acquired BSI (CA – BSI):** Bactériémie communautaire identifiée dans les 48H00 suivant l'admission à l'hôpital chez un patient sans exposition récente au système de santé
- **Healthcare-associated BSI:** Bactériémie associée aux soins identifiée dans les 48H00 suivant l'admission à l'hôpital chez un patient exposé au système de soins à savoir dialysé chronique, vivant en milieu médicalisé, avec une exposition récente aux antibiotiques.
- **Hospital-acquired BSI:** Bactériémie acquise à l'hôpital: identifiée dans les 48H00 après l'admission à l'hôpital
- **ICU-acquired BSI:** Bactériémie identifié dans les 48H00 après l'admission en réanimation

Introduction

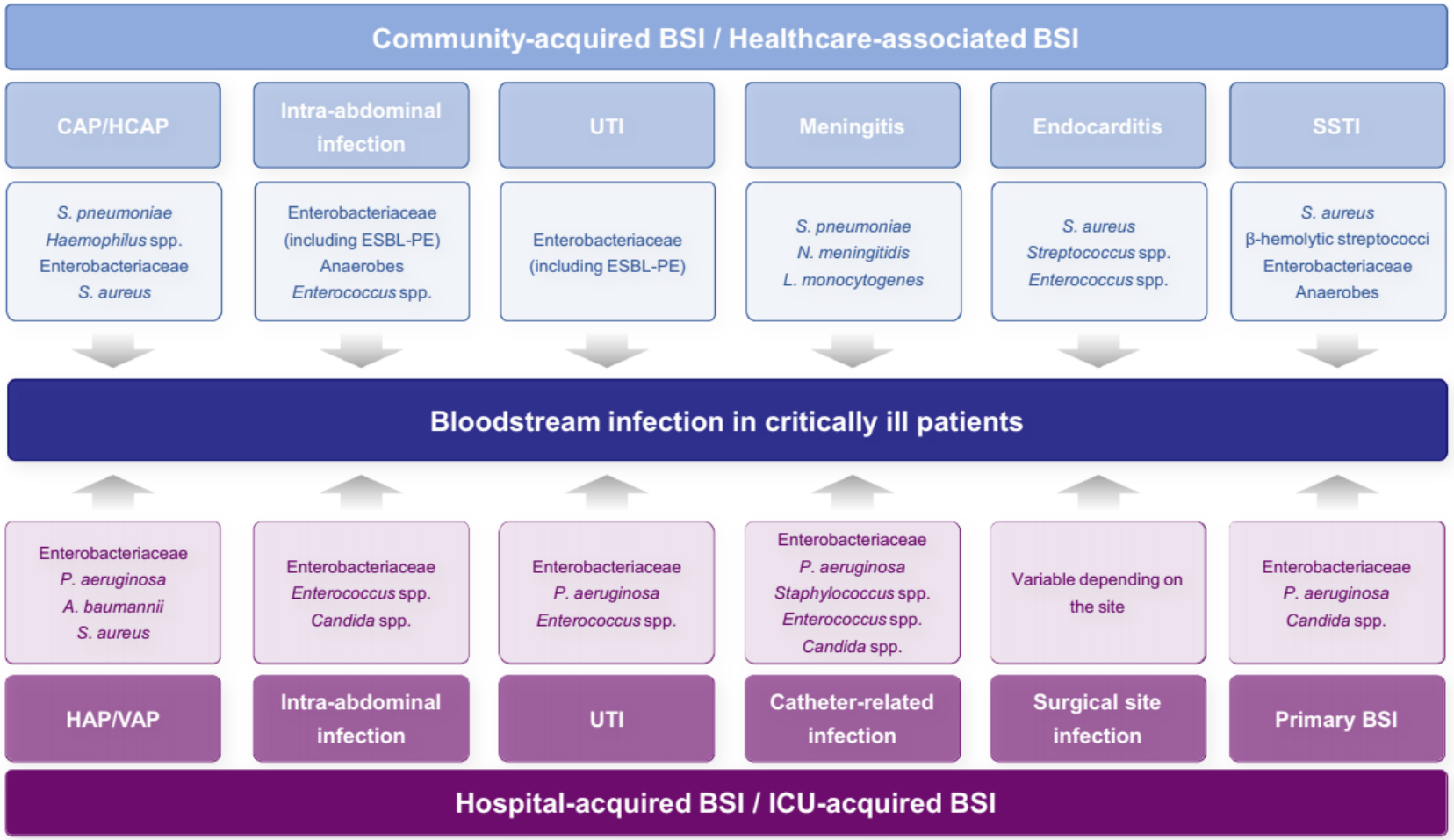
5% des patients en réanimation vont présenter une bactériémie

Entre 30 et 40% des patients admis pour sepsis ou choc septique en réanimation présente une bactériémie

Mortalité entre 35 et 50% en réanimation

Timsit, ICM, 2020

Principales sources et germes en cause

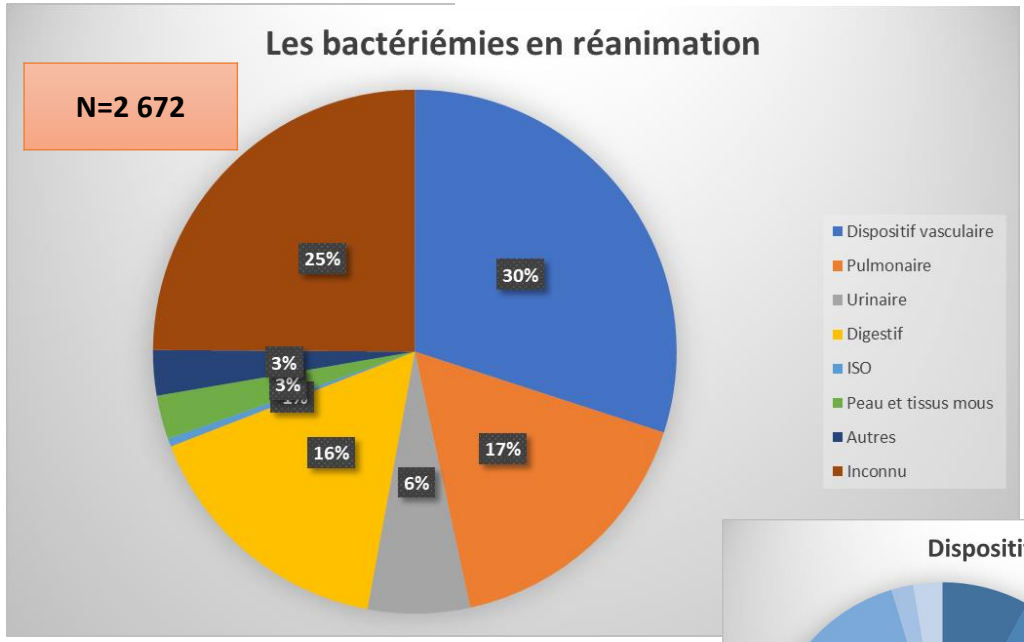


Timsit, ICM, 2020

- ***BSI*** bloodstream infection,
- ***CAP*** community-acquired pneumonia,
- ***HCAP*** healthcare-associated pneumonia,
- ***UTI*** urinary tract infection,
- ***ESBL-PE*** extended-spectrum beta-lactamase-producing Enterobacterales,
- ***SSTI*** skin and soft-tissue infection,
- ***HAP*** hospital-acquired pneumonia,
- ***VAP*** ventilator-associated pneumonia.

Réa raisin 2014 et Eurobact

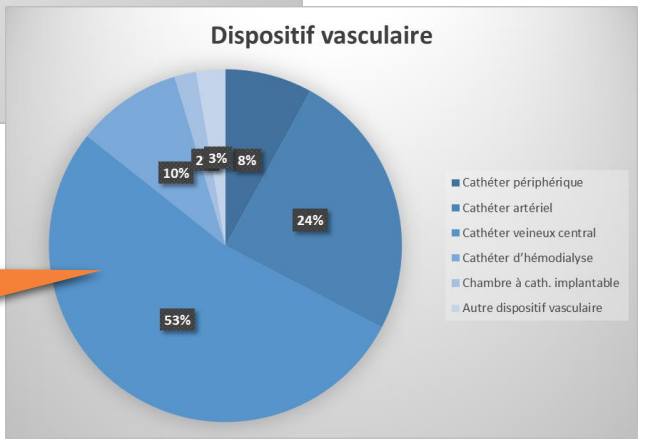
- En 2015:
  - 3.64/100 patients surveillés
  - 3.52 pour 1000 j de séjour en réanimation
- ↗ taux incidence des bactériémies entre 2004 et 2015 de 3.31 à 3.52 pour 1000 j de séjour en réanimation (+6.3%,pval=0.07)



Dans Eurobact (n=1156):

- 21% infections sur dispositif vasculaire
- 21% pneumopathie
- 12% infection intra abdominale
- 24% pas de source retrouvée

Souvent origine KT, abdo, respi et non identifiée



Tabah, ICM, 2012

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Original Article

Effect of SARS-CoV-2 infection and pandemic period on healthcare-associated infections acquired in intensive care units

Alain Lepape [1, 2, 3, *], Anaïs Machut [2, 4], Cedric Bretonnière [2, 5], Arnaud Friggeri [1, 2, 3], Charles-Hervé Vacheron [1, 2], Anne Savey [2, 3, 4], on behalf of REA-REZO network

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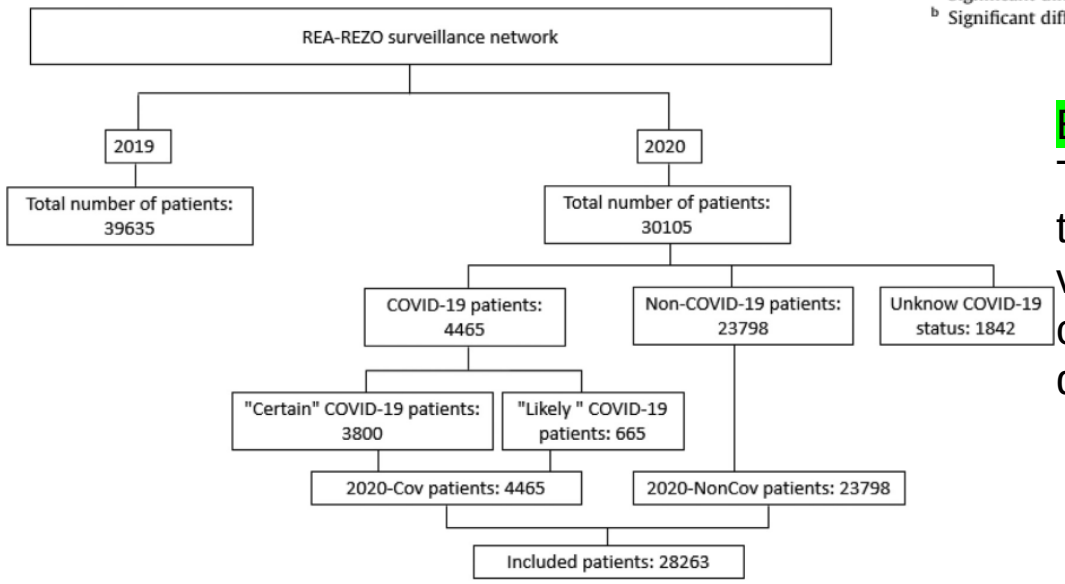


Fig. 1. Flowchart. 2020NonCov, non–COVID-19; 2020Cov, COVID-19 group.

Table 2
Healthcare-associated infections acquired in intensive care units

	2019Control 39 635	2020NonCov 23 798	2020Cov 4465	p
Patients with at least one infection, *n* (%)	3698 (9.3 [9.04–9.61])	2680 (11.3 [10.86–11.66])	1160 (26 [24.69–27.27])	<0.001[a,b]
Pneumonia (including VAP), *n* (%)	2852 (7.2 [6.94–7.45])	2140 (9 [8.63–9.36])	1024 (22.9 [21.70–24.17])	<0.001[a,b]
VAP, *n* (%)	2507 (10.4 [10.01–10.78])	1948 (12.9 [12.34–13.41])	973 (37 [35.18–37.88])	<0.001[a,b]
VAP/1000 d of MV	15.4 (14.78–15.97)	18.4 (17.62–19.24)	35.6 (33.42–37.81)	<0.001[a,b]
Interval from MV onset to VAP (d), median (IQR)	8 (4–13)	7 (4–12)	8 (5–13)	<0.001[a,b]
Bloodstream infection	1271 (3.2 [3.03–3.38])	888 (3.7 [3.49–3.97])	388 (8.7 [7.86–9.52])	<0.001[a,b]
Blood stream infection/1000 d of stay	3.4 (3.33–3.45)	3.9 (3.84–3.88)	6.4 (6.36–6.44)	<0.001[a]
Central catheter-related bacteraemia, *n* (%)	163 (0.6 [0.52–0.70])	118 (0.6 [0.57–0.81])	36 (1.2 [0.83–1.62])	<0.001[a]
Central catheter-related bacteraemia/1000 central catheter d	0.6 (0.47–0.65)	0.6 (0.58–0.65)	0.6 (0.63–0.63)	NS

Data are shown as the number of patients n and percentage (%) or median and interquartile range (IQR). Between-group comparisons with significant p value set at 0.001.2020NonCov, non–COVID-19; 2020Cov, COVID-19 group; MV, mechanical ventilation; NS, not significant; VAP, ventilator-associated pneumonia.
[a] Significant difference between 2020Cov and 2020NonCov.
[b] Significant difference between 2020NonCov and 2019Control.

Bloodstream infection

The increase in BSI rate in the 2020Cov group compared with the 2019NonCov group was related to an increase in intra-vascular device origin of infection, particularly from peripheral catheters, but also from pulmonary origin, whereas bacteraemia of digestive origin were less frequent (Table 4).

major effect on the hospital organization, with work overload, creation of temporary beds in ICUs, involvement of personnel not usually dedicated to ICUs, and an initial shortage of personal protective equipment

Table 4
Origin of bacteraemia of each origin

	2019Control (*N* = 1271)	2020NonCov (*N* = 1030)	2020Cov (*N* = 466)
Intra-vascular devices n (%)	404 (27.5)	38.4	35.7
Arterial catheter	107 (7.3)	123 (11.9)	43 (9.2)
Peripheral catheter	38 (2.6)	81 (7.9)	48 (10.3)
Central venous catheter	201 (13.7)	146 (14.2)	60 (12.9)
PICC	8 (0.5)	8 (0.8)	2 (0.4)
Haemodialysis catheter	26 (1.8)	18 (1.7)	6 (1.3)
Implantable port catheter	13 (0.9)	3 (0.3)	0 (0.0)
ECMO	5 (0.3)	4 (0.4)	3 (0.6)
Midline	—	3 (0.3)	3 (0.6)
Other vascular devices	6 (0.4)	9 (0.9)	2 (0.4)
Lungs, *n* (%)	272 (18.5)	151 (14.7)	114 (24.5)
Urinary tract, *n* (%)	102 (6.9)	47 (4.6)	19 (4.1)
Digestive tract, *n* (%)	242 (16.5)	109 (10.5)	26 (5.6)
SSI, *n* (%)	7 (0.5)	4 (0.4)	2 (0.4)
Skin and soft tissues infections, *n* (%)	57 (3.9)	24 (2.3)	3 (0.6)
Other origin, *n* (%)	15 (1.0)	9 (0.9)	5 (1.1)
Unknown, *n* (%)	369 (25.1)	291 (28.3)	130 (27.9)

2020NonCov, non–COVID-19; 2020Cov, COVID-19 group; ECMO, extracorporeal circulation membrane oxygenation; PICC, peripherally inserted central catheter; SSI, surgical site infection.

Les germes des CA-BSI en réanimation

!!!! ↗
Entérobactérie
BLSE

- Variation en fonction des pays, régions, hôpitaux, source de l'infection, caractéristiques du patient
  - Dans 70% des cas : E Coli, S Aureus, K Pneumoniae et S Pneumoniae
  - 5% de pseudomonas en communautaire surtout chez les patients immunodéprimés, ou bactériémies liées aux soins, ou origine urinaire ou respiratoire
  - Très peu de souche BMR
    - SARM en plateau
    - Entérobactérie BLSE en augmentation en communautaire, jusqu'à 5% des infections urinaires, intra abdominales – voire 20% dans certaines régions

Timsit, ICM, 2020

Les HA-BSI en réanimation

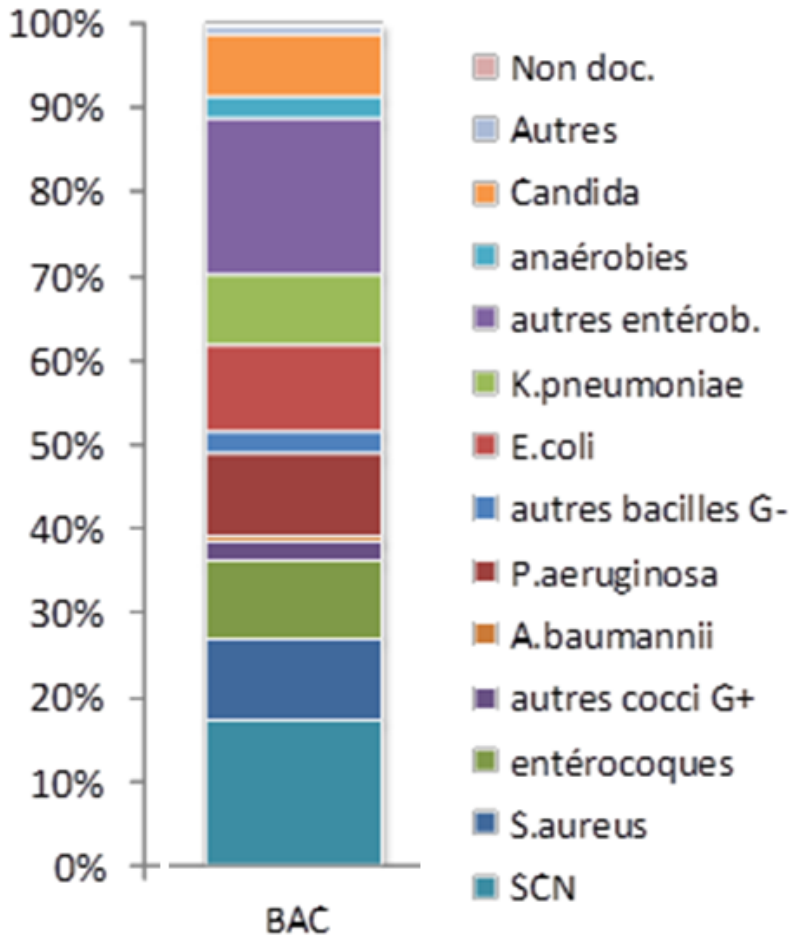
Dispositif invasif	Densité d'incidence pour 1000 cathéter-jours
CVC	0.5 et 2.5 épisodes
Cathéter artériel	1 épisode
ECMO	20 épisodes

- 25% importés/75% acquise en réanimation
- 5 à 7% des patients admis en réanimation présentent une ICU-acquired BSI
- Facteurs de risques de ICU-acquired BSI :
  - Sévérité, durée de séjour prolongée, immunosuppression, pathologie hépatique, admission chirurgie, matériel invasif
- Épidémiologie des MDR varie d'une réanimation à l'autre
  - P. aeruginosa and Acinetobacter baumannii surtout dans les pays chauds
  - Sinon surtout ESBL-PE, carba-PE, MDR P. aeruginosa, MDR Acinetobacter baumannii, SARM et methicillin-resistant coagulase-negative staphylococci

ESBL-PE : Extended-spectrum beta-lactamase-producing Enterobacteriaceae (ESBL-PE)
MDR: MultiDrug Resistance
SARM: staphylocoque aureus méticilline résistant
Carba-PE: Carbapenemase-producing

Timsit, ICM, 2020

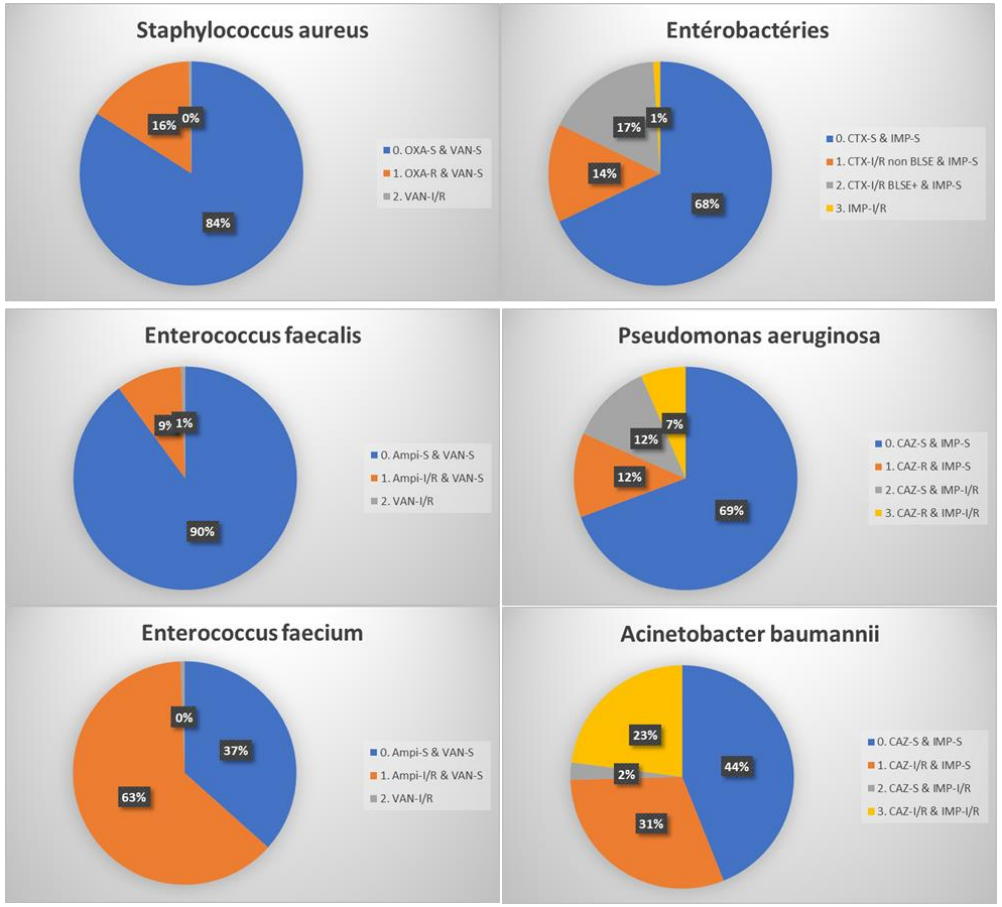
Répartition des micro-organismes



Timsit, ICM, 2020

Germes	HA-BSI	ICU-BSI
Escherichia coli	10-19%	4-10%
Klebsiella spp.	8-9%	4-15%
Enterobacter spp.	5-7%	1-8%
Pseudomonas aeruginosa	7-10%	2-12%
Acinetobacter baumannii	3-7%	2-16%
Staphylococcus aureus	16-26%	6-27%
CoNS	10-20%	13-39%
Enterococcus spp.	9-11%	8-19%
Candida spp.	7-10%	6-15%
Autres	<5-24%	3-19%

Indicateurs de résistance

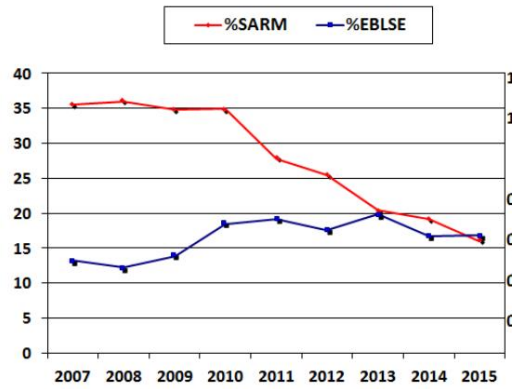


Timsit, ICM, 2020; Réa Raisin

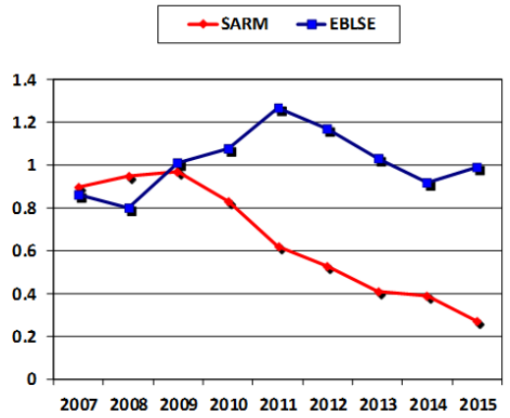
Table 4 Current resistance rates in major pathogens responsible for hospital-acquired infections according to World Health Organization regions—available data from large surveillance networks

Resistant isolates (%) among invasive isolates of a given species	WHO regions				
	Americas	Europe	Eastern Mediterranean	South-East Asia	Western Pacific
Escherichia coli/resistance to ESC	16–22	28–36	11–41	20–61	0–77
Klebsiella pneumoniae/resistance to ESC	21–56	41–62	17–50	53–100	27–72
Klebsiella pneumoniae/resistance to carbapenems	9–11	0–4	0–54	0–52	0–8
Pseudomonas aeruginosa/MDR phenotype	18–20	NA	30–36	34–43	30–35
Acinetobacter baumannii/resistance to carbapenems	47–64	0–23	60–70	26–65	62–72
Staphylococcus aureus/resistance to methicillin	42–55	33–95	13–53	2–81	4–84

ESC extended-spectrum cephalosporins, *MDR* multidrug-resistant



Pourcentage de résistance dans l'espèce ou la famille

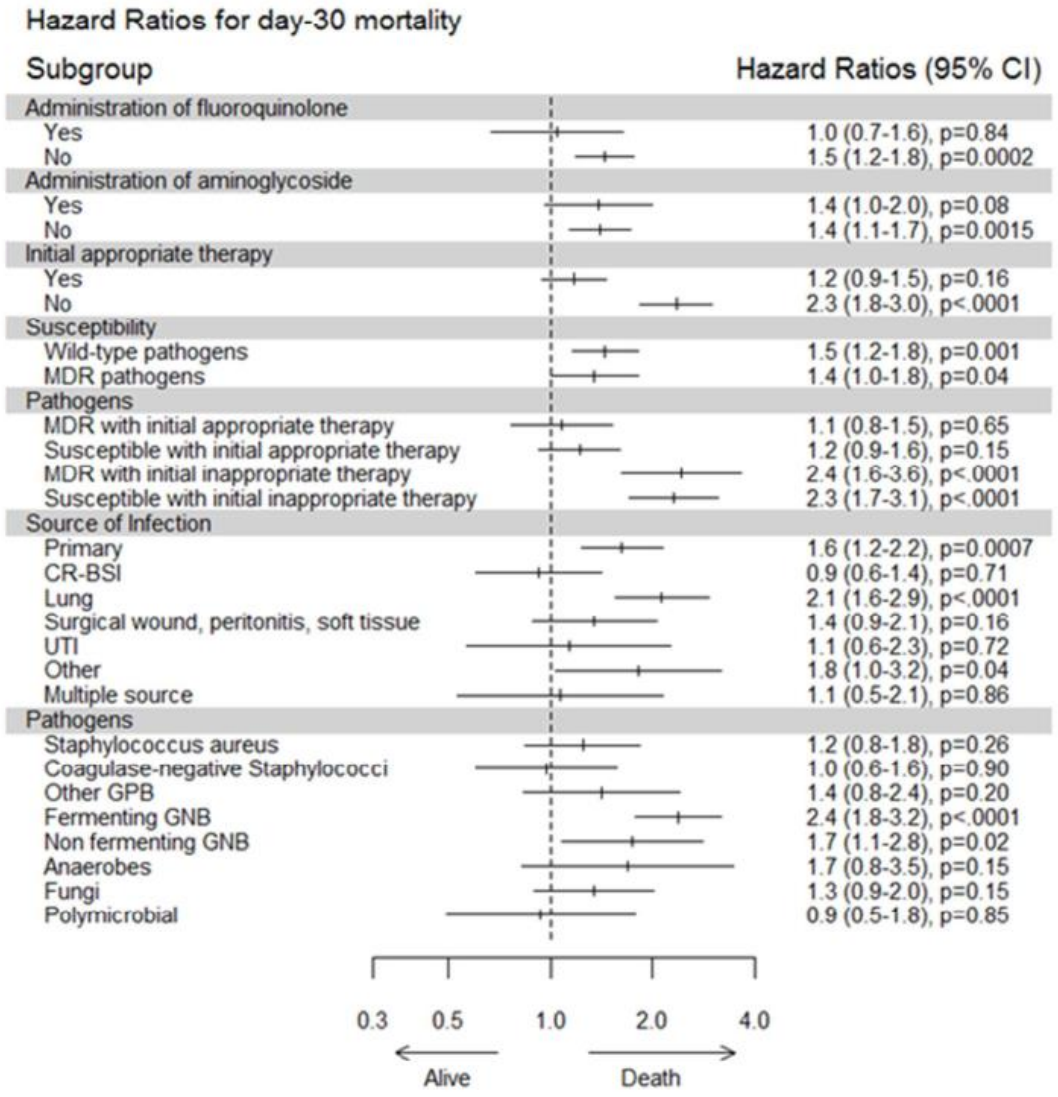


Taux Incidence cumulée des IN à SARM et EBLSE / 100 patients

N=571

Attributable mortality of ICU-acquired Bloodstream Infections: impact of the source, causative micro-organism, resistance profile and antimicrobial therapy

Dr Christophe Adrie, MD, PhD, Maité Garrouste-Orgeas, MD, PhD, Wafa Ibn Essaied,



ICU-BSI

↗ **risque décès:** HR, 1.40; 95% CI, 1.16 to 1.69; p < 0.01.

↗ de 130% quand pas d'adéquation initiale: HR, 2.3; 95% IC, 1.8 à 3.0;

↗ 20% quand adéquation initiale: HR, 1.2; 95% IC, 0.9 à 1.5

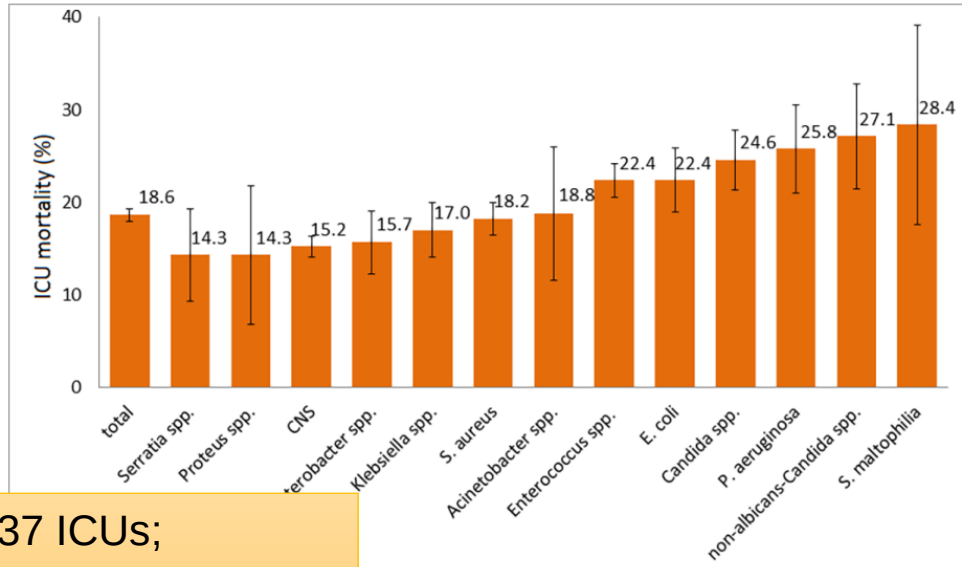
Adrie, Journal of Infection, 2016

PLOS ONE

RESEARCH ARTICLE

ICU mortality following ICU-acquired primary bloodstream infections according to the type of pathogen: A prospective cohort study in 937 Germany ICUs (2006-2015)

Frank Schwab[1,2]*, Christine Geffers[1,2], Michael Behnke[1,2], Petra Gastmeier[1,2]



4,556,360 patients avec 16,978,882 patient jour de 937 ICUs;
14,626 BSI dont 12,745 mono-microbiennes

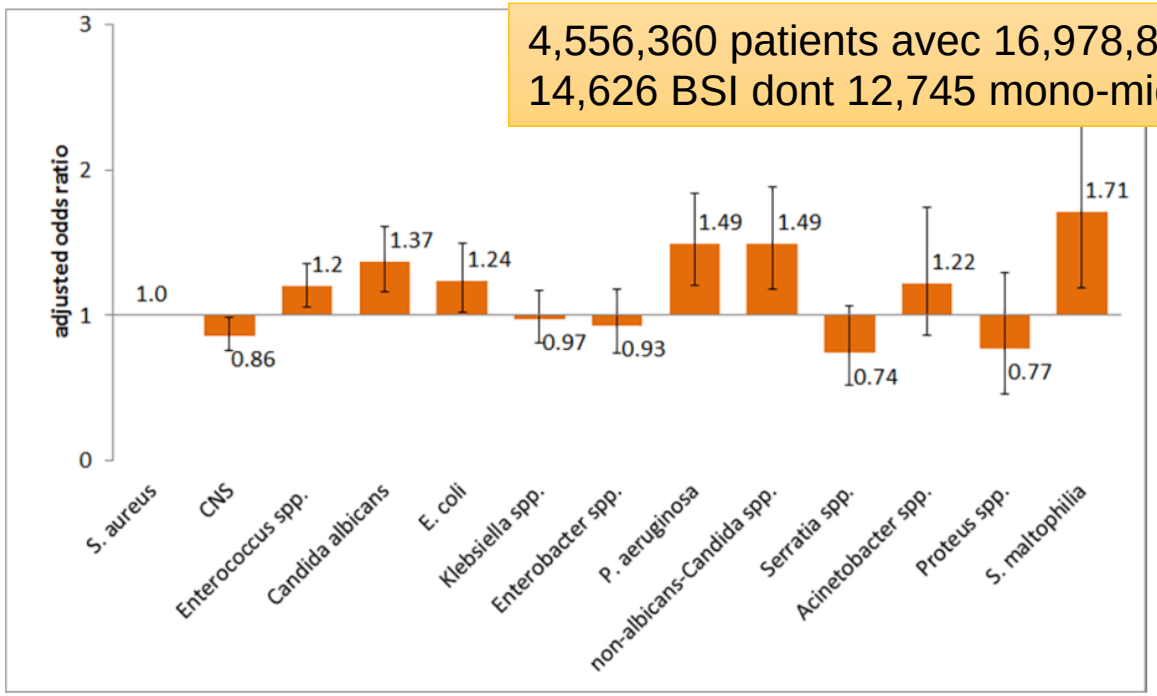
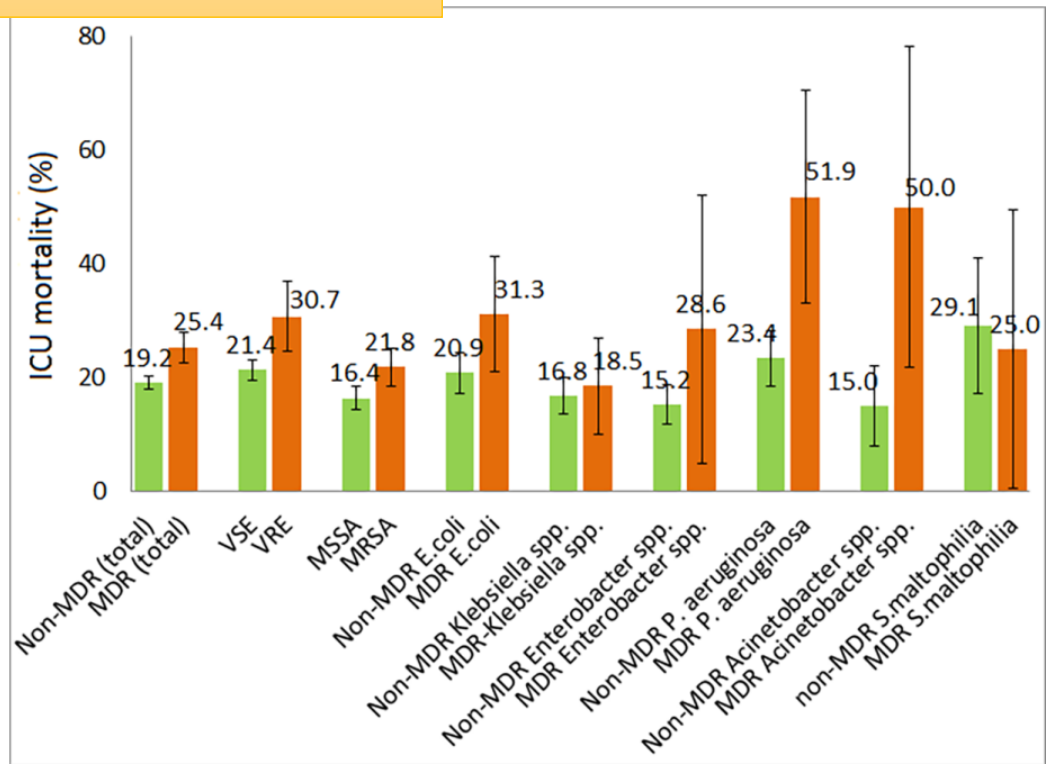


Fig 3. Adjusted odds ratios (AOR) for ICU mortality in patients with ICU-acquired primary bloodstream infections according to the type of pathogen. ICU, intensive care unit; CNS, coagulase negative staphylococci; Whiskers represent 95% confidence interval; S. aureus was set as reference.



Schwab, Plos one, 2017

Buetti *et al. Critical Care* (2022) 26:319
https://doi.org/10.1186/s13054-022-04166-y

Critical Care

RESEARCH Open Access

Different epidemiology of bloodstream infections in COVID-19 compared to non-COVID-19 critically ill patients: a descriptive analysis of the Eurobact II study

Niccolò Buetti[1,2*], Alexis Tabah[3,4,5], Ambre Loiodice[6], Stéphane Ruckly[6], Abdullah Tarik Aslan[7], Giorgia Montrucchio[8,9], Andrea Cortegiani[10,11], Nese Saltoglu[12], Bircan Kayaaslan[13], Firdevs Aksoy[14], Akova Murat[15], Özlem Akdoğan[16], Kemal Tolga Saracoglu[17], Cem Erdogan[18], Marc Leone[19], Ricard Ferrer[20], José-Artur Paiva[21,22], Yoshiro Hayashi[23], Mahesh Ramanan[24,25,26], Andrew Conway Morris[27,28,29], François Barbier[30,31], Jean-François Timsit[2,32] and the Eurobact 2 study group

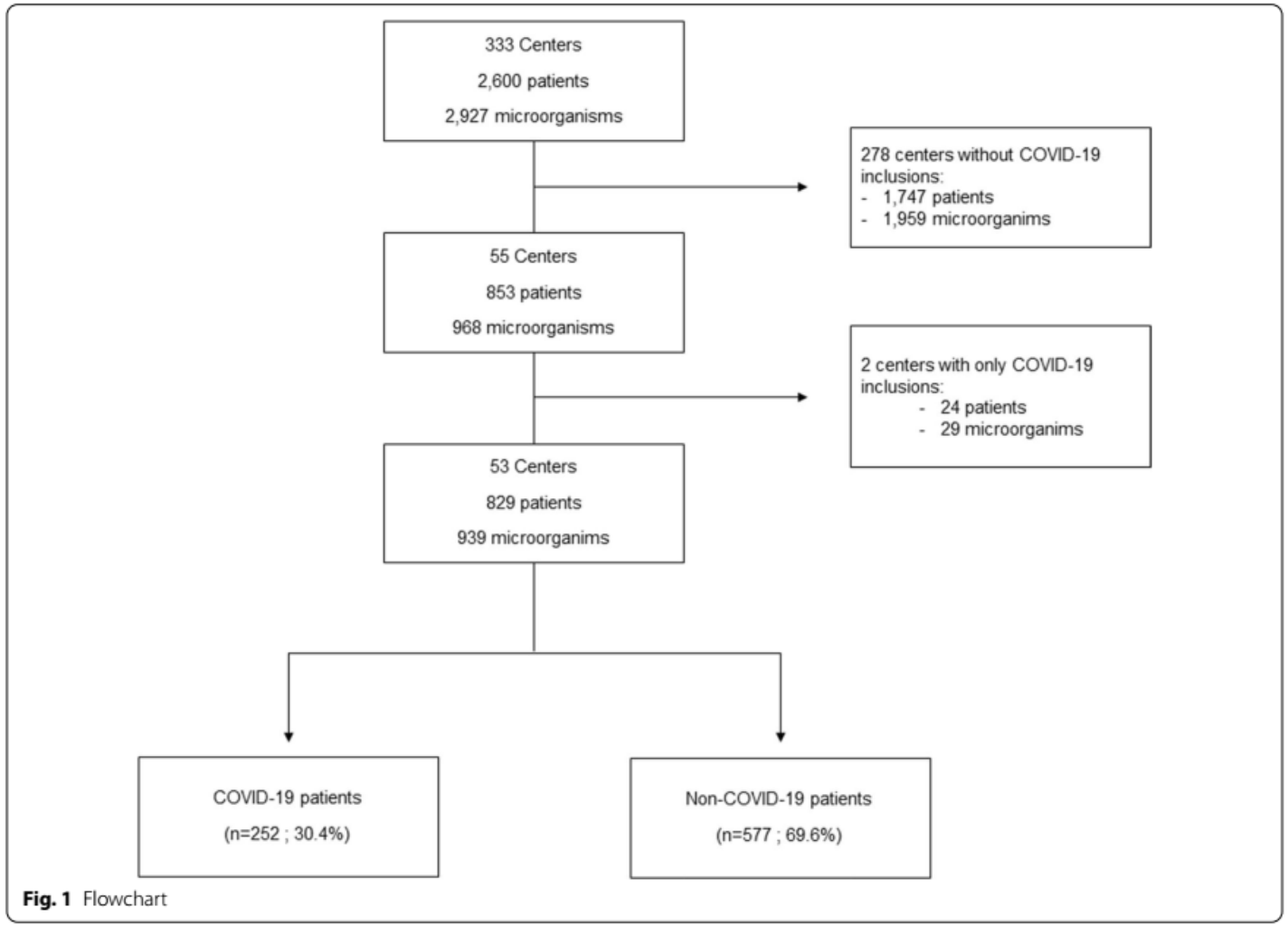


Fig. 1 Flowchart

Abstract

Background: The study aimed to describe the epidemiology and outcomes of hospital-acquired bloodstream infections (HABSIs) between COVID-19 and non-COVID-19 critically ill patients.

Methods: We used data from the Eurobact II study, a prospective observational multicontinental cohort study on HABSI treated in ICU. For the current analysis, we selected centers that included both COVID-19 and non-COVID-19 critically ill patients. We performed descriptive statistics between COVID-19 and non-COVID-19 in terms of patients' characteristics, source of infection and microorganism distribution. We studied the association between COVID-19 status and mortality using multivariable fragility Cox models.

Results: A total of 53 centers from 19 countries over the 5 continents were eligible. Overall, 829 patients (median age 65 years [IQR 55; 74]; male, $n = 538$ [64.9%]) were treated for a HABSI. Included patients comprised 252 (30.4%) COVID-19 and 577 (69.6%) non-COVID-19 patients. The time interval between hospital admission and HABSI was similar between both groups. Respiratory sources (40.1 vs. 26.0%, $p < 0.0001$) and primary HABSI (25.4% vs. 17.2%, $p = 0.006$) were more frequent in COVID-19 patients. COVID-19 patients had more often enterococcal (20.5% vs. 9%) and *Acinetobacter* spp. (18.8% vs. 13.6%) HABSIs. Bacteremic COVID-19 patients had an increased mortality hazard ratio (HR) versus non-COVID-19 patients (HR 1.91, 95% CI 1.49–2.45).

Conclusions: We showed that the epidemiology of HABSI differed between COVID-19 and non-COVID-19 patients. Enterococcal HABSI predominated in COVID-19 patients. COVID-19 patients with HABSI had elevated risk of mortality.

Trial registration ClinicalTrials.org number NCT03937245. Registered 3 May 2019.

Keywords: Bloodstream infection, ICU-acquired, COVID-19, *Enterococcus*, Bacteremia

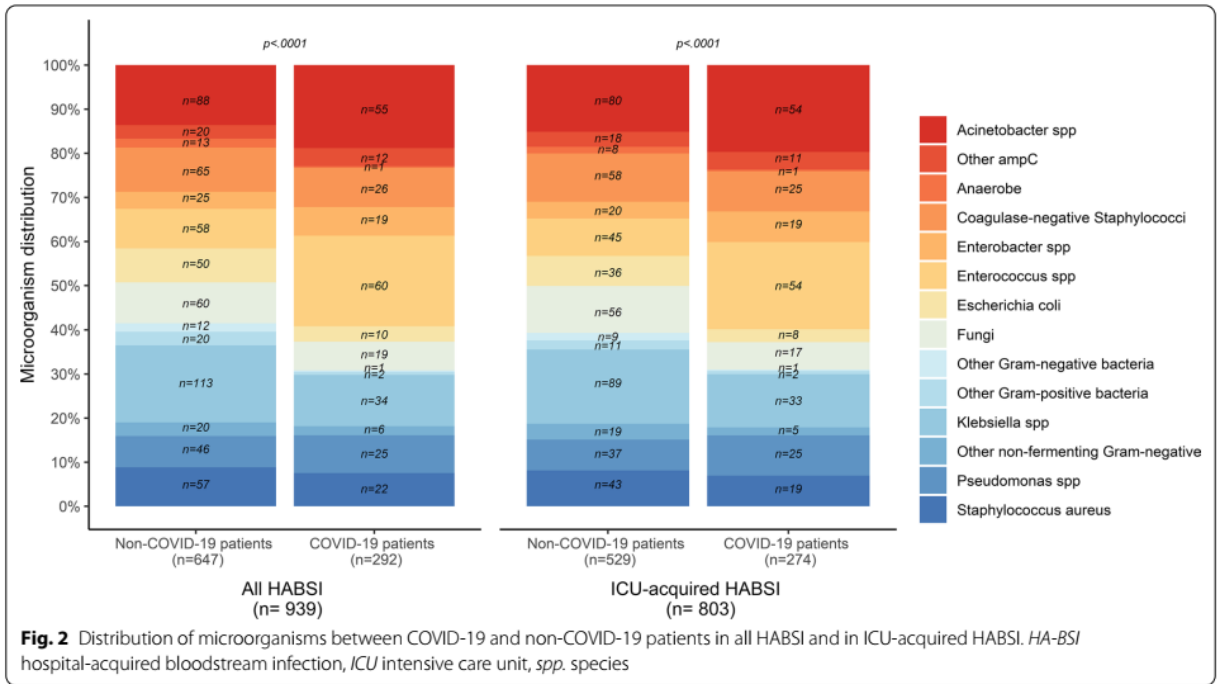


Fig. 2 Distribution of microorganisms between COVID-19 and non-COVID-19 patients in all HABSI and in ICU-acquired HABSI. *HA-BSI* hospital-acquired bloodstream infection, *ICU* intensive care unit, *spp.* species

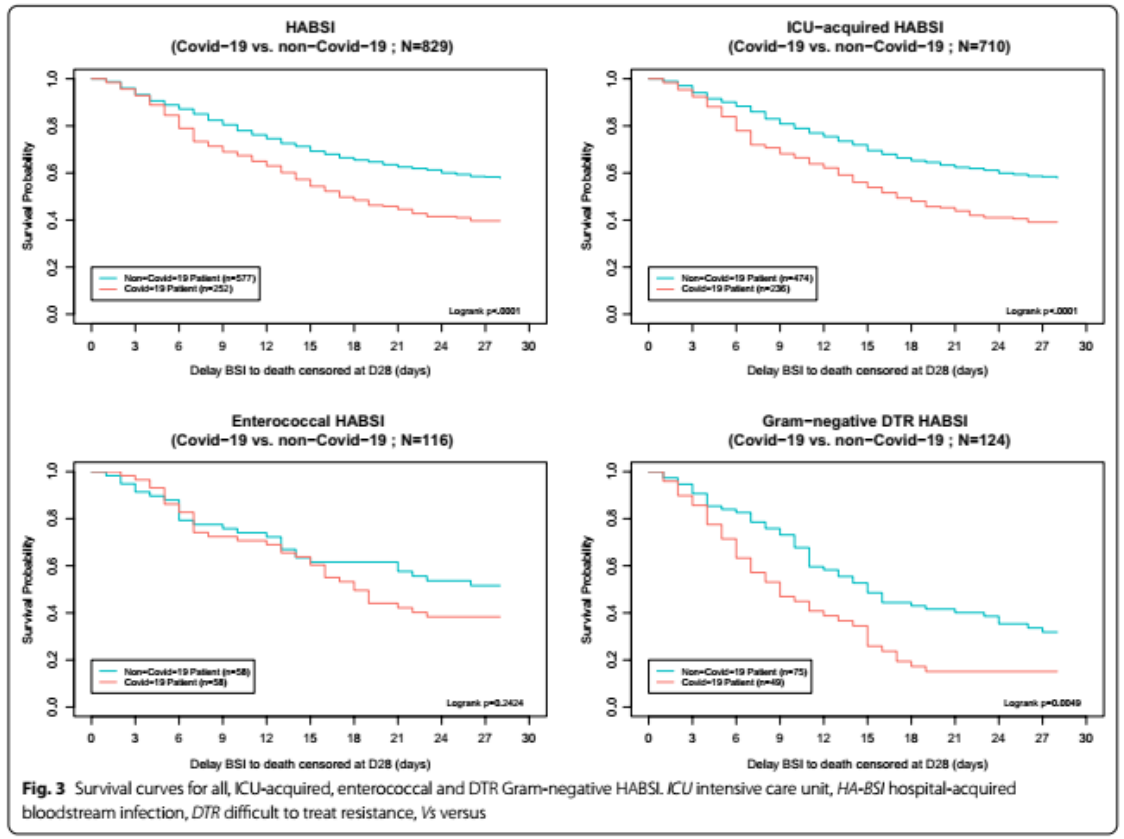
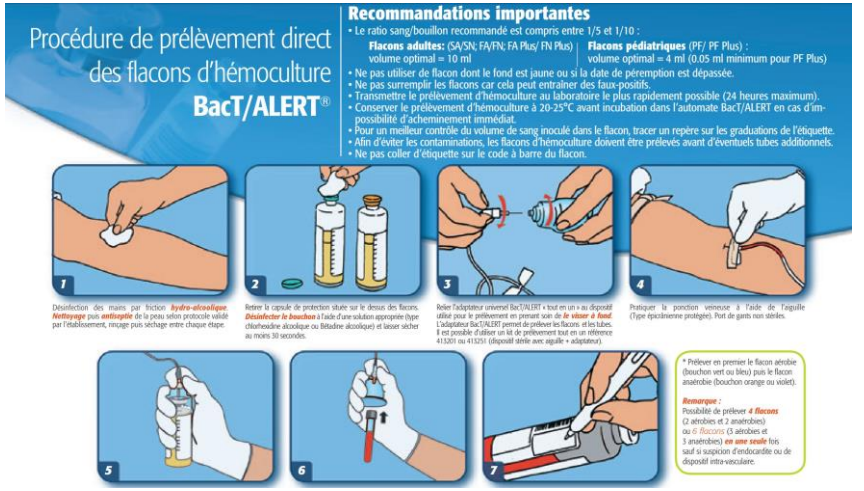


Fig. 3 Survival curves for all, ICU-acquired, enterococcal and DTR Gram-negative HABSI. *ICU* intensive care unit, *HA-BSI* hospital-acquired bloodstream infection, *DTR* difficult to treat resistance, *Vs* versus

Diagnostic et bilan d’extension

Identification - diagnostic



- Bactériémie = hémocultures positives en dehors des contaminations
- Inoculation sang dans des flacons d'hémocultures anaérobies et aérobies mis en incubation
- 2 à 3 paires d'hémocultures bien remplis (10 mL) avant antibiothérapie sur 2 sites différents ou espacés d'au moins 30 minutes
- En cas de suspicion d'endocardite, les espacer dans le temps
- Si suspicion infection sur cathéter: prélever paires hémocultures sur cathéters et en périphérie
- Avant toute antibiothérapie sauf purpura fulminans
- Quand faire les hémocultures:
  - En cas de fièvre +/- frissons intenses, sueurs, hypotension inexpliquée,
  - Foyers infectieux multiples ou
  - Patient neutropénique ou porteur de matériel étranger,
  - Hypothermie,
  - En l'absence de fièvre si sujet âgé, immunodéprimé, corticothérapie, traitement antipyrétique

Lamy, Frontiers in microb, 2016

Contamination?

- Parmi l'ensemble des hémocultures prélevées dans un hôpital seul 3 à 5% sont positives
- Parmi ces hémocultures, 20 à 56% sont positives à des contaminants
- Bactérie de la flore cutanée: Staphylocoques coagulase négative (SCN), corynebacterium spp., Micrococcus spp, Bacillus spp, Propionibacterium acnes …
- Délai de pousse allongé
- **Attention particulière si:**
  - Matériel, quel qu'il soit, notamment endovasculaire
  - Contexte clinique: porte entrée cutanée, toxicomanie, neutropénie
  - Certaines bactéries: staphylococcus lugdunensis (pouvoir pathogène proche de S. aureus), corynebacterium jeikeium (infection de matériel chez l'immunodéprimé notamment).
- **Ce n'est pas une contamination si:**
  - Plusieurs hémocultures au même germe
  - Hémoculture positive à plusieurs germes possible si foyer digestif, fistule vasculaire, neutropénie
  - Une seule hémoculture positive à un germe qui est toujours pathogène: Staphylococcus aureus, streptococcus pneumoniae, Escherichia Coli, autres entérobactéries, pseudomonas, listeria, pasteurella, candida…

Lamy, Frontiers in microb, 2016

Caractériser la bactériémie

- **Distinguer:**
  - La porte d'entrée (plaie cutanée, muqueuse, inoculation, translocation digestive)
  - Le foyer infectieux (pneumonie, pyélonéphrite, colite, méningite…)
  - Les localisations secondaires (abcès rénal, spondylodiscite …)
  - Les relais endovasculaires (endocardite, thrombophlébite septique, infection de prothèse endovasculaire …)
  - CA-BSI – HCA-BSI – HA-BSI – ICU-acquired BSI
- **Et toujours rechercher:**
  - Les signes de gravités (sepsis, choc septique)
  - Le terrain (neutropénie +++)

Les méthodes de diagnostic rapide

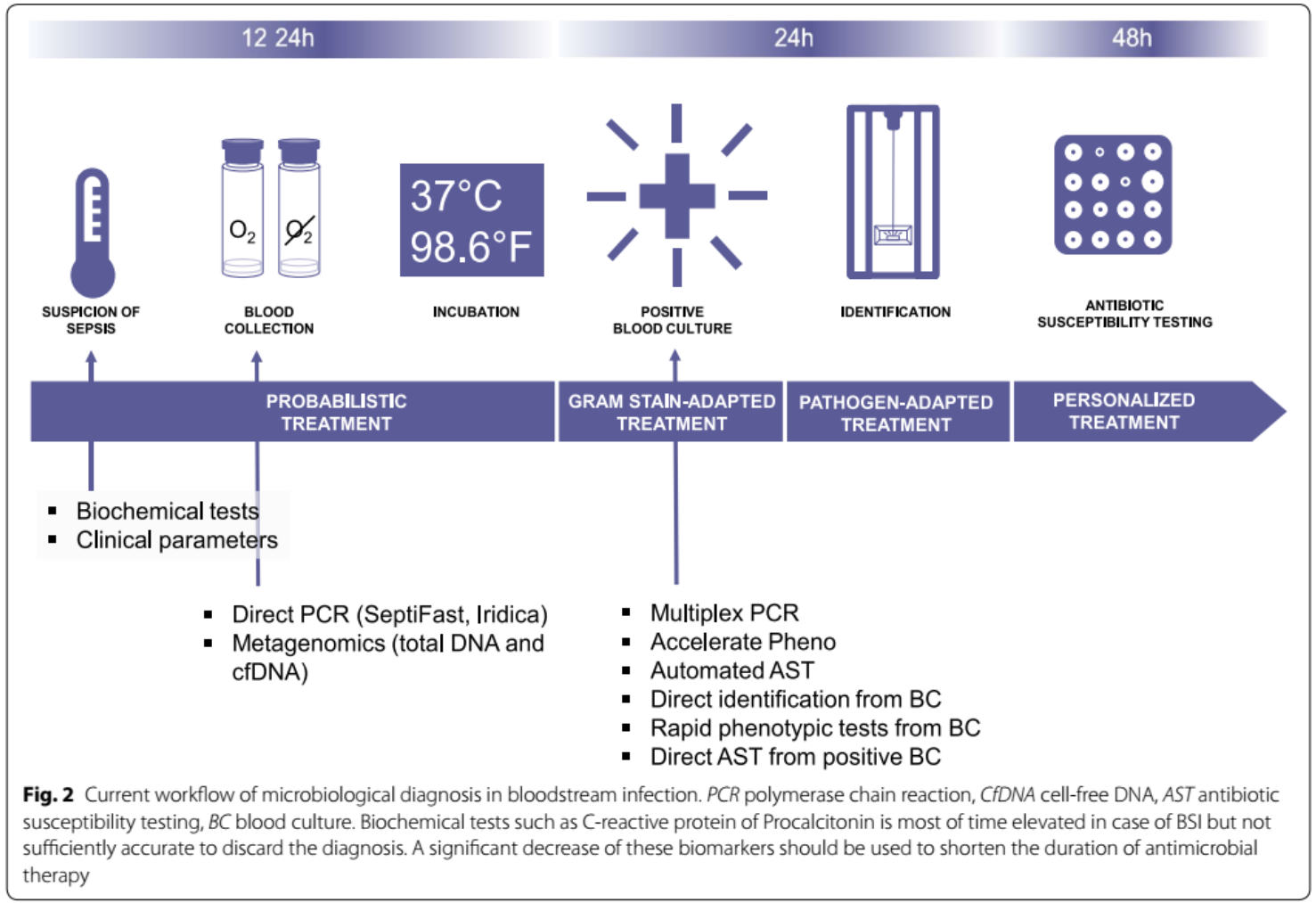


Fig. 2 Current workflow of microbiological diagnosis in bloodstream infection. *PCR* polymerase chain reaction, *CfDNA* cell-free DNA, *AST* antibiotic susceptibility testing, *BC* blood culture. Biochemical tests such as C-reactive protein of Procalcitonin is most of time elevated in case of BSI but not sufficiently accurate to discard the diagnosis. A significant decrease of these biomarkers should be used to shorten the duration of antimicrobial therapy

Timsit, ICM, 2020

- 48H00 pour Antibiogramme
- PCR direct sur sang
  - Sn et Sp médiocre
  - automates non disponible
  - pas tous les mécanismes de résistances
- Tests reposant sur des techniques de résonnance magnétiques : T2Bacteria Panel, T2Biosystems → Meilleur Sn (90%): rendu en 3.5h à 5 à 8 heures
- Tests PCR sur Hémocultures positives → excellente performance
- Matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF) : slt sur culture + après purification de l'échantillon bonne performance pour les BGN (> 90% concordance) mais moins pour CGP (slt 80%); peux détecter certains mécanisme de résistance
- Plus récemment: next-generation sequencing (NGS) methods → avenir

Bilan d'extension

- Hémocultures persistantes
  - Faire échographie/doppler des axes vasculaires, imagerie pour les emboles septiques (angioTDM corps entier) et échocardiographie (surtout si staphylocoque doré, streptocoque (sauf groupe A), entérocoque, candida), fond d'oeil
- Hémocultures persistantes à S. Aureus ou entérocoque
  - Faire ETO
- Hémocultures persistante et risque EI
  - Faire ETO, quel que soit le germe si:
    - Hémodialyse, foyers emboliques d'infection, toxicomanie IV, chambre implantable, dispositif électronique intracardiaque, valve prothétique, ATCD Ei et anomalie structurelle cardiaque.

RFE SRLF 2019

Prise en charge thérapeutique

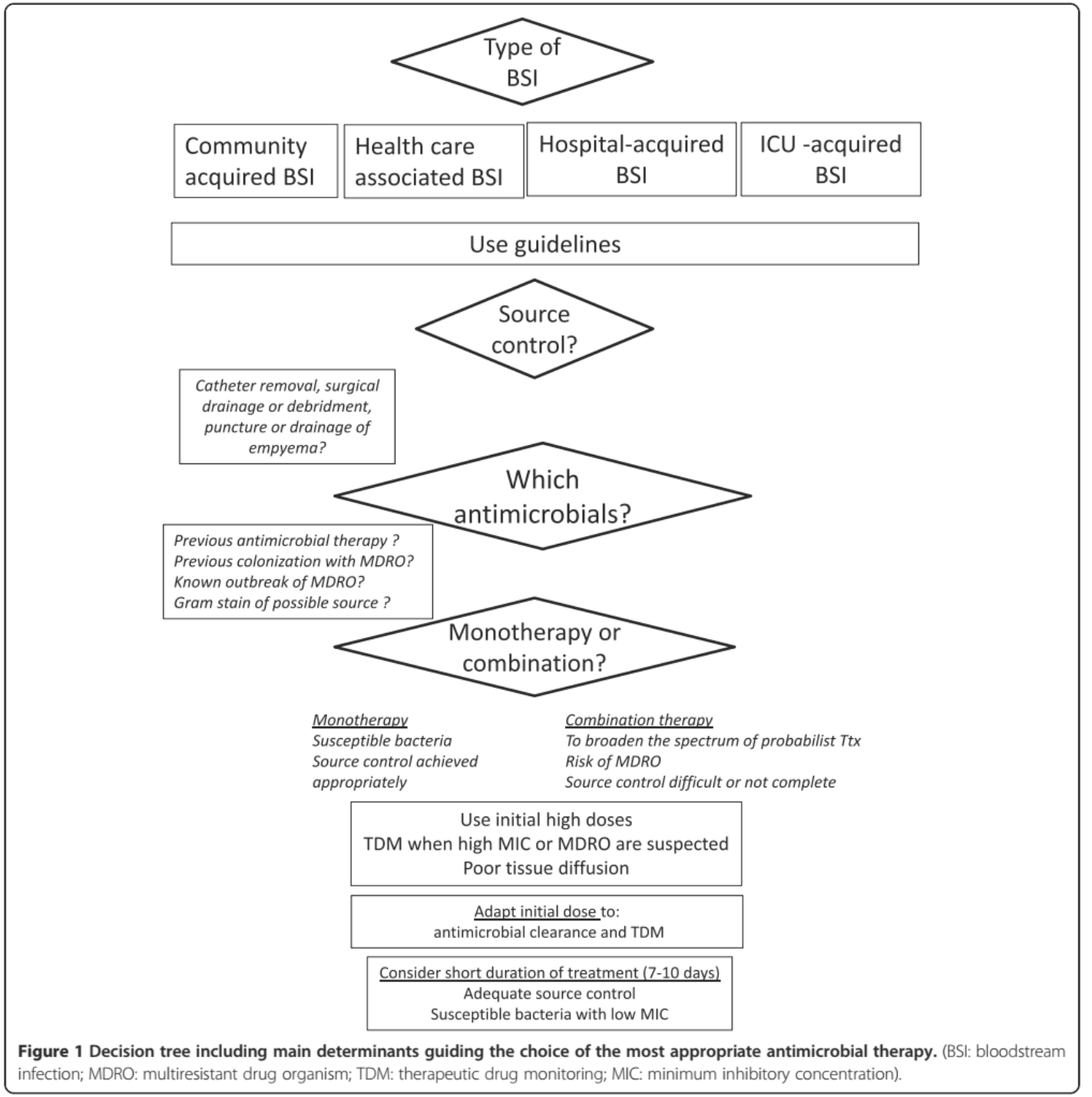


Figure 1 Decision tree including main determinants guiding the choice of the most appropriate antimicrobial therapy. (BSI: bloodstream infection; MDRO: multiresistant drug organism; TDM: therapeutic drug monitoring; MIC: minimum inhibitory concentration).

Timsit, BMC Infectious Diseases, 2014

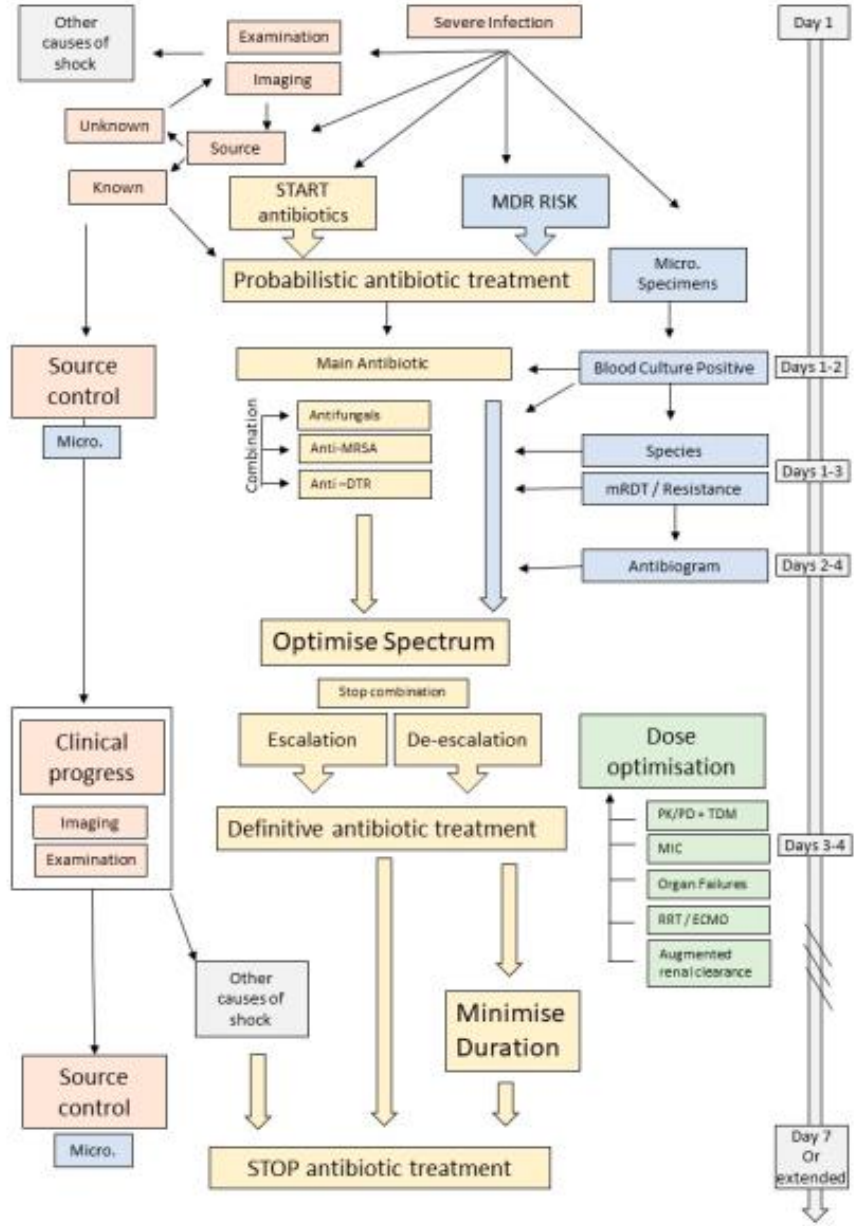


Figure 1. Management of an ICU patient with a blood stream infection. mRDT = molecular rapid diagnostic testing, Micro. = microbiology specimens, MDR = multidrug resistant, DTR = difficult-to-treat resistance, MRSA = methicillin-resistant *Staphylococcus aureus*.

Tabah, antibiotics, 2022

Time to antibiotics

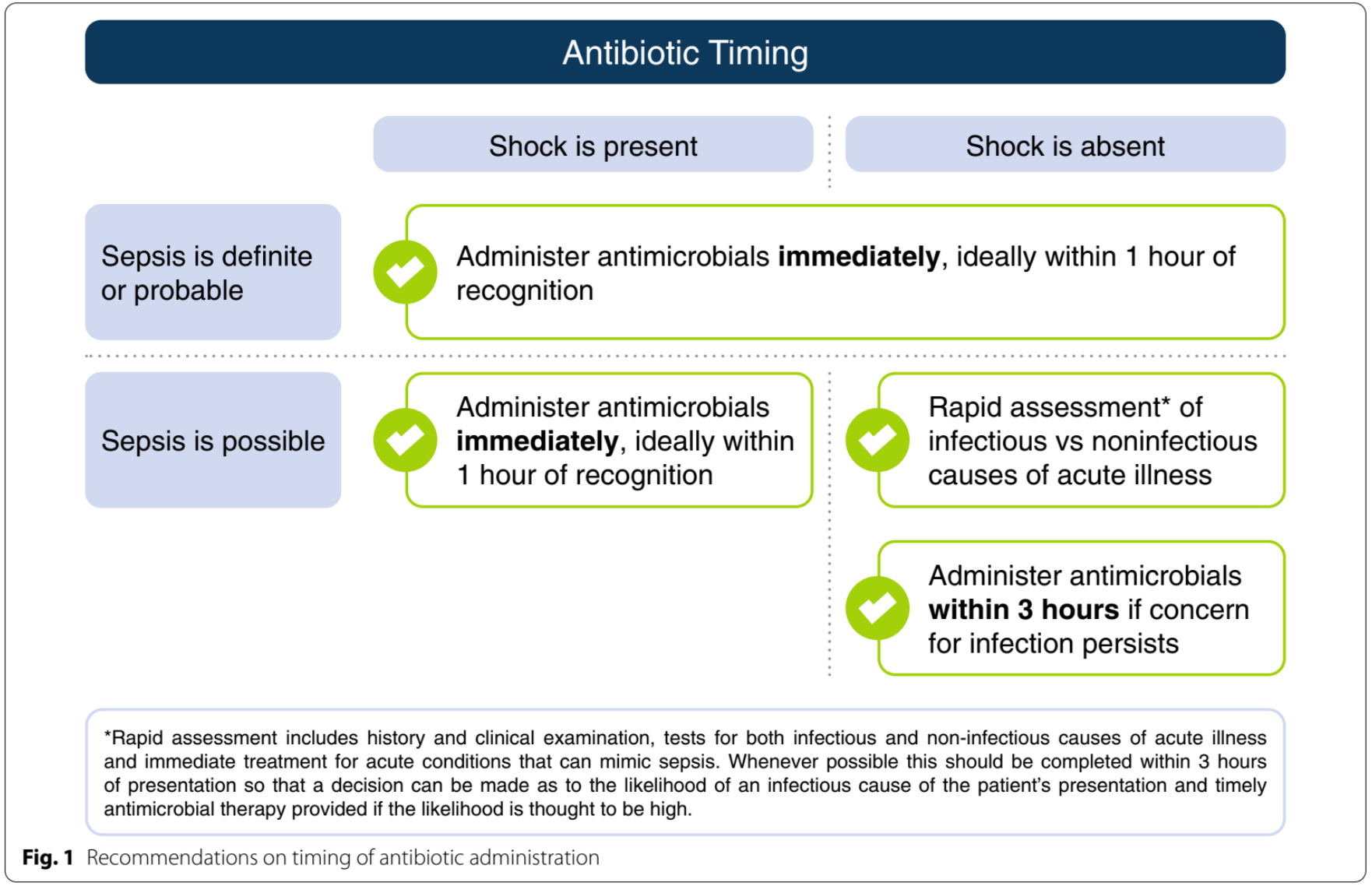


Fig. 1 Recommendations on timing of antibiotic administration

Evans, ICM, 2021

Contrôle de la source

- Péritonite, obstacle urinaire, dermo-hypodermite nécrosante, pleurésie, péricardite, empyèmes, abcès profond…
- Argument pour drainage/débridement
  - Diminution de l'inoculum
  - Diminution du risque de récidive
  - Diminution du risque de sélection de mutants résistants
  - Accélère le traitement d'un territoire dans lequel la diffusion antibiotique est mauvaise
  - Effet symptomatique antalgique selon les cas

Choix du traitement anti-microbiens

1. Traitement empirique ou documenté
2. Origine de l'infection présumée ou prouvée
3. Suspicion ou présence avérée de résistances
4. Immunosupression
5. Suspicion ou candidémie avérée

- Toujours évaluer la balance bénéfice risque
  - ATB large spectre et sélection de résistances
  - ATB plus ciblée mais risque d'échec thérapeutique et/ou retard d'instauration d'une ATB efficace
- !!! Stratégie d'épargne des nouvelles beta-lactamines
- Raisonner en fonction de l'écologie locale, du patient (colonisation, exposition ATB, voyage), et des pratiques de services.

Timsit, ICM, 2020

Table 1. Most common pathogen groups according to the presumed source of infection.

	Urinary	Respiratory	Intra-Abdominal	Intra Vascular Catheter
Community acquired	Enterobacterales *Enterococcus* sp. *P. aeruginosa* *	*Streptococcus pneumoniae* ++ *Legionella* sp. *** Enterobacterales *S. aureus* *P. aeruginosa* * *H. influenzae*	Enterobacterales *Enterococcus* sp. *Candida* sp. Anaerobes Polymicrobial	Coagulase neg. staphylococci *S. aureus* Enterobacterales
Hospital acquired	Enterobacterales *Candida* sp. *Enterococcus* sp. *P. aeruginosa* *Acinetobacter* sp.	Enterobacterales *S. aureus* *P. aeruginosa* *Acinetobacter* sp.	Enterobacterales *P. aeruginosa* *Enterococcus* sp. *Candida* sp. Anaerobes Polymicrobial	Enterobacterales *S. aureus* Coagulase neg. staphylococci *P. aeruginosa* *Acinetobacter* sp.

Describes the most common pathogens. Non-exhaustive list. ++ Largely predominant. * In patients with chronic respiratory disease and patients with long-term indwelling catheter for respiratory and urinary sources, respectively. *** *Legionella* sp. does not cause BSIs but should be included in severe community-acquired respiratory infections.

Tabah, antibiotics, 2022

Risques de bactériémies à BMR

Table 2. Risk factors for multidrug-resistant bacteria.

Individual factors (history)	Recent hospitalisation (1 year) Exposure to antimicrobials (3–6 months) Severe co-morbidities (Charlson ≥ 4) Recent immunosuppression Chronic respiratory disease (COPD, cystic fibrosis) Recurrent urinary tract infections Urinary catheter
Individual factors (current)	Prior duration of hospital and ICU stay (continuous increase over time) High severity Known colonisation (surveillance cultures and previous infections)
Institution factors	Regional/institutional prevalence of MDR Overwhelmed health systems

COPD = chronic obstructive pulmonary disease, MDR = multidrug resistant, ICU = intensive care unit.

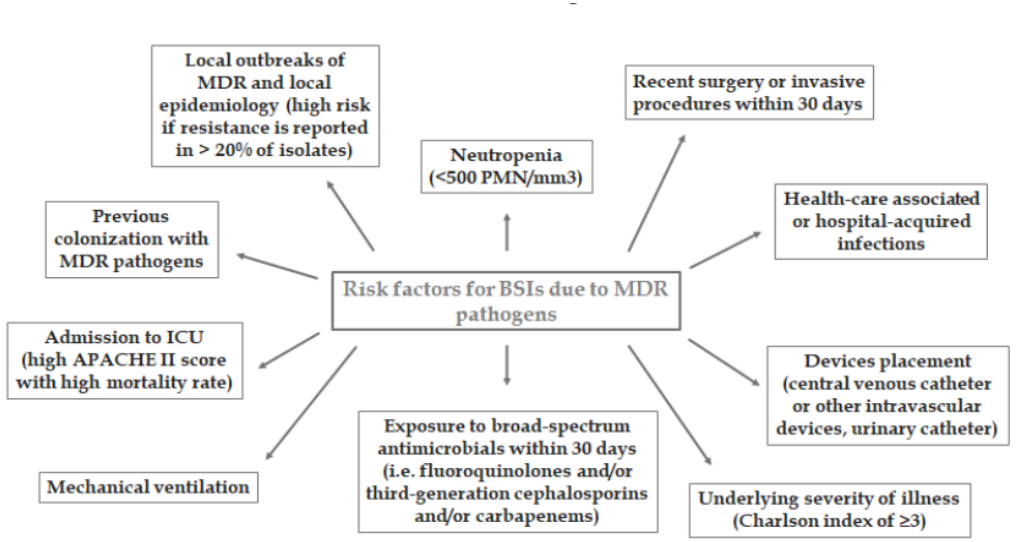


Figure 1. Risk factors for BSIs due to MDR pathogens.

Tabah, antibiotics, 2022; Di Franco, Life, 202

Choix du traitement anti-microbiens

Table 6 Characteristics of antibacterial drugs indicated (or used off-label in selected cases) for treating bloodstream infections (BSI) in critically ill patients

Antibacterials	Activity against MDR pathogens	Class, PD index of choice Suggested dosage in critically-ill patients	Status
Amikacin	Possibly active against MDR-GNB, although increased resistance to classical aminoglycosides has been reported [79, 143]	Aminoglycosides, AUC/MIC 25-30 mg/kg q24h (modified according to TDM)	Approved
Aztreonam	Active against MBL producers not expressing mechanisms of aztreonam resistance (e.g., other beta-lactamases, AmpC hyperexpression, efflux pumps)	Monobactams, T > MIC 1–2 g q8h	Approved
Aztreonam/Avibactam	ESLBL-PE CPE (all classes of carbapenemases, including MBL)	Monobactams plus BLI, T > MIC 6500 mg aztreonam/2167 mg avibactam q24h on day 1 followed by 6000 mg aztreonam/2000 mg avibactam q24h	In clinical development; potential indications according to phase-3 RCT are cIAI, HAP/VAP (NCT03329092) and serious infections due to MBL-producing bacteria (NCT03580044)
Cefepime	Active against AmpC hyperproducer enterobacterales	Cephalosporins, T > MIC 2 g q8h or continuous infusion	Approved
Cefiderocol	ESBL-PE CPE (all classes of carbapenemases, including MBL) MDR-PA CRAB	Siderophore cephalosporins, T > MIC 2 g q8h	FDA Approved for cUTI caused by susceptible Gram-negative microorganisms, who have limited or no alternative treatment options according to phase-3 RCT are infections due to carbapenem-resistant organisms in different sites (NCT02714595). Pivotal study on HAP/VAP finished (NCT03032380)
Ceftobiprole	MRSA VISA hVISA VRSA	Cephalosporins, T > MIC 500 mg q8 h	Approved for CAP and HAP (excluding VAP) *In vitro* and/or limited clinical data reporting a possible use as salvage therapy in combination with vancomycin or daptomycin for MRSA bacteremia
Ceftolozane/Tazobactam	ESBL-PE MDR-PA	Cephalosporins plus BLI, T > MIC 1.5 g q8h (3 g q8h for pneumonia)	Approved for cIAI (in combination with metronidazole) and cUTI Approved by FDA for VAP/HAP, with the CHMP of EMA also recently adopting a positive opinion recommending a change to the terms of the marketing authorization, including also VAP/HAP among approved indications
Ceftaroline	MRSA VISA hVISA VRSA	Cephalosporins, T > MIC 600 mg q12 h	Approved for ABSSSI and CAP In vitro and/or limited clinical data reporting a possible use as salvage therapy in combination with vancomycin or daptomycin for MRSA bacteremia
Ceftazidime		Cephalosporins, T > MIC 6 g q24h continuous infusion	Approved
Ceftazidime/Avibactam	ESBL-PE CPE (class A and class D carbapenemases) MDR-PA	Cephalosporins plus BLI, T > MIC 2.5 g q8h	Approved for cIAI (in combination with metronidazole), cUTI, HABP/VABP, and infections due to aerobic Gram-negative organisms in adult patients with limited treatment options
Ceftriaxone		Cephalosporins, T > MIC 1–2 g q24h	Approved
Colistin	ESBL-PE CPE (all classes of carbapenemases, including MBL) MDR-PA CRAB	Polymyxins, AUC/MIC 9 MU loading dose, 4.5 MU every 8–12 h (modified according to TDM where available; higher dosages to be possibly considered in patients with ARC [58])	Approved Recommended for serious infections due to susceptible bacteria when other treatment options are limited
Daptomycin	MRSA VRE	Lipopeptides, AUC/MIC 8–10 mg/kg q24h	Approved for cSSTI and right-sided endocarditis
Eravacycline	MRSA VRE ESBL-PE CPE CRAB	Fluocyclines, AUC/MIC 1 mg/kg q12h	Approved for cIAI To be possibly used for BSI due to MDR organisms in absence of dependable alternative options, in combination with other agents (expert opinion)
Ertapenem	ESBL-PE	Carbapenems, T > MIC 1 g q12 h	Approved for IAI, CAP, acute gynecological infections, and diabetic food infections
Fosfomycin	ESBL-PE CPE (all classes of carbapenemases, including MBL) MDR-PA MRSA VRE	PEP analogues, unclear [144] 4–6 g q6h continuous infusion	Approved For BSI used in combination with other agents for the treatment of MDR infections with limited treatment options (also for CRAB), although in lack of high-level evidence
Gentamicin	Possibly active against MDR-GNB, although increased resistance to classical aminoglycosides has been reported [79, 143]	Aminoglycosides, AUC/MIC 5–7 mg/kg q24h (modified according to TDM)	Approved
Imipenem/Cilastatin	ESBL-PE	Carbapenems, T > MIC 0.5–1 g q6h	Approved
Imipenem/Relebactam	ESBL-PE CPE (class A carbapenemases) Some MDR-PA	Carbapenems plus BLI, T > MIC 500 mg/250–125 mg q6h	FDA approved for the treatment of cUTI and cIAI. The phase-3 RCT are HAP/VAP (NCT02493764) is ongoing.
Meropenem	ESBL-PE	Carbapenems, T > MIC 1–2 g q8h or extended infusion (over 4 h)	Approved
Meropenem/Vaborbactam	ESBL-PE CPE (class A carbapenemases)	Carbapenems plus BLI, T > MIC 4 g q8h	Approved for cUTI, cIAI, HAP, VAP, and infections due to aerobic Gram-negative organisms in patients with limited treatment options
Piperacillin/Tazobactam	Possibly active against ESBL-PE, although the results of the MERINO trial discourage the use of piperacillin/tazobactam for severe ESBL-PE infections [145]	Penicillins plus BLI, T > MIC 4.5 g q6h continuous infusion	Approved
Plazomicin	ESBL-PE CPE (all classes of carbapenemases, including MBL, although resistance has been described in NDM-1 producing strains, owing to co-expression of plazomicin-inactivating methyltransferases [146]) MDR-PA CRAB	Aminoglycosides, AUC/MIC 15 mg/kg q24h	An application has been recently submitted to EMA for approval of plazomicin for cUTI and other severe infections (plazomicin is approved by FDA for cUTI)
Tigecycline	MRSA VRE ESBL-PE CPE (all classes of carbapenemases, including MBL) CRAB	Glycylcyclines, AUC/MIC 100–200 mg loading those, then 50–100 mg q12h	Approved for cSSTI (excluding diabetic foot infections) and cIAI For BSI used only in combination with other agents for infections due to MDR organisms in presence of limited alternative therapeutic options
Vancomycin	MRSA	Glycopeptides, AUC/MIC 15–30 mg/kg loading dose, 30–60 mg/kg q12h, or continuous infusion (modified according to TDM)	Approved

ABSSSI acute bacterial skin and skin-structure infections, *ARC* augmented renal clearance, *AUC* area under the concentration curve, *BLI* beta-lactamases inhibitors, *BSI* bloodstream infections, *CAP* community-acquired pneumonia, *CHMP* Committee for Medicinal Products for Human Use, *cIAI* complicated intra-abdominal infections, *CPE* carbapenemase-producing *Enterobacterales*, *CRAB* carbapenem-resistant *Acinetobacter baumannii*, *cSSTI* complicated skin and soft-tissue infections, *cUTI* complicated urinary tract infections, *EMA* European Medicines Agency, *ESBL-PE* extended-spectrum beta-lactamase-producing *Enterobacterales*, *FDA* Food and Drug Administration, *HAP* hospital-acquired pneumonia, MBL metallo-beta-lactamases, *NDM* New Delhi metallo-beta-lactamase, *L-AmB* liposomal amphotericin B, *MDR* multidrug-resistant, *MIC* minimum inhibitory concentration, *MRSA* methicillin-resistant *Staphylococcus aureus*, *MU* million units, *PA Pseudomonas aeruginosa*, *PD* pharmacodynamics, *PEP* phosphoenolpyruvate, *RCT* randomized controlled trials, *TDM* therapeutic drug monitoring, *VAP* ventilator-associated pneumonia, *VRE* vancomycin-resistant enterococci

Timsit, ICM, 2020

Table 3. Targets and dosing strategies for most commonly used antibiotics.

Antimicrobial	Specific Targets	Dosing Strategies	Caution
Beta-lactam antibiotics			
Ampicillin–sulbactam	CRAB	9 g q8h (CI/EI)	High dosing increases risk of neurotoxicity
Ampicillin or amoxicillin	Narrow-spectrum targeted therapy	2 g q6h (II)	
Amoxicillin–clavulanic acid	Narrow-spectrum targeted therapy CA-peritonitis	2 g/200 mg q6h (II)	
Piperacillin–tazobactam	Broad-spectrum antipseudomonal probabilistic for HAI	4.5 g q6h EI/CI preferred, loading dose req.	Biliary excretion Resistance promotion
Antistaphylococcal molecules			
Flucloxacillin	MSSA	2 g q4–6h (II/CI)	
Cefazolin	MSSA	2 g q8h	
Ceftaroline	MRSA/VISA/VRSE	600 mg q8h	Neutropenia especially in longer treatments
Ceftobiprole	MRSA, MRSE, non-MDR GNB	500 mg q8h (2h EI)	Q4–6 h depending on degree of ARC Dose adjust in renal impairment
Vancomycin	MRSA/MRSE/*E. faecium*	LD 30 mg/kg followed by 30 mg/kg (CI) or 15 mg/kg q12h(II)	TDM required
Daptomycin	MRSA/MRSE/VRE	8–10 mg/kg q24h	
Linezolid	MRSA/MRSE/VRE	600 mg q12h	
Cephalosporins			
Ceftriaxone	CAP Susceptible Enterobacterales	1 g q12h EI	
Cefotaxime	CAP Susceptible Enterobacterales	1 g q6h EI CI suggested	
Ceftazidime	*Pseudomonas* sp., *Acinetobacter* sp.	2 g q8h ((EI/CI)	
Cefepime	AmpC-Es	2 g q8h EI	MIC ≥ 4 risk of ESBL-Es and treatment failure Most neurotoxic β-lactam, especially in overdose
Cefiderocol	CREs (KPCs, OXA48, MBLs), DTR-PA	2 g q8h EI (3 h)	Poor efficacy for CRAB
Carbapenems			
Imipenem-cilastatin	Broad spectrum Probabilistic for HAI Targeted ESBL-Es	1 g q6–8h (II)	
Meropenem	*Pseudomonas* sp., *Acinetobacter* sp.	1–2 g q8h (II, EI, CI)	Poor efficacy against *Enterococcus* sp.
Ertapenem	ESBLE-Es	1–2 g/24 h (II)	
New combinations *			
Ceftazidime–avibactam	CREs (KPCs, OXA-48)	2 g/500 mg q8h (II/EI)	
Aztreonam (+CAZ-AVI)	MBL-CREs, DTR-PA, *Stenotrophomonas maltophilia*	2 g q8h	Infuse aztreonam at same time with CAZ-AVI
Ceftolozane–tazobactam	DTR-PA	2 g/1 g q8h (II)	
Aztreonam–avibactam	MBL-CREs	2 g/500 mg q8h (II)	
Meropenem–vaborbactam	KPC-CREs, DTR-PA	2 g/2 g q8h IV (II/EI)	
Imipenem–relebactam	KPC-CREs, DTR-PA	500 mg/250 mg q6h (II)	
Aminoglycosides	Combination to extend spectrum when at risk for MDR. ESBL-Es, AmpC-Es, CREs, CRAB, DTR-PA.	Once-Daily dose	Nephrotoxicity Ototoxicity TDM required
Amikacin		25–30 mg/kg (/24h)	
Gentamicin		7–8 mg/kg (/24h)	
Polymyxins	CREs (KPCs, OXA48, MBLs) CRAB, DTR-PA Resistant to new/targeted antibiotics		Last-line antimicrobials Nephrotoxicity Use TDM if available
Polymyxin B	Systemic infections	Loading dose 2–2.5 mg/ kg (20,000–25,000 IU/kg) 12-hourly injections of 1.25–1.5 mg/kg (12,500–15,000 IU/kg TBW)	Not renally adjusted Very few data on DTR BSIs
Colistin (CMS)	Urinary source	Loading dose of 300 mg CBA (9 MUI) then 12–24 h later: 300–360 mg CBA/day (9–10 MUI/day) divided in 2 injections	Renally adjusted More nephrotoxicity than polymyxin B
Other classes			
Ciprofloxacin	ESBL-Es, AmpC-Es, MDR-PA, *Stenotrophomonas maltophilia*	400 mg q8–12h (II/EI)	
Fosfomycin	CREs (KPCs, OXA48, MBLs) CRAB, DTR-PA		Salvage therapy if susceptible Combination if possible
Tigecycline	CREs (KPCs, OXA48, MBLs) CRAB	100 mg LD then 50 mg q12h OR 200 mg (LD) then 100 mg q12h	Caution with coagulopathy if high dose Use as part of combination
Eravacycline	CREs (KPCs, OXA48, MBLs), CRAB	1 mg/kg q12h (II)	
Cotrimoxazole (TMP/SMX)	ESBL-Es, AmpC-Es, *Stenotrophomonas maltophilia*	1.2–1.6 g SMX q8h (II)	

BSI = blood stream infection, HAI = hospital-acquired infections, CA = community acquired, CAP = community-acquired pneumonia, MDR = multidrug resistant, DTR = difficult-to-treat resistance, MSSA = methicillin-susceptible *Staphylococcus aureus*, MRSA = methicillin-resistant *Staphylococcus aureus*, VISA = vancomycin-intermediate *Staphylococcus aureus*, VRSE = vancomycin-resistant *Staphylococcus aureus*, VRE = vancomycin-resistant *Enterococcus*, PA = *Pseudomonas aeruginosa*, ESBL-Es = ESBL-producing Enterobacterales, CREs = carbapenem-resistant Enterobacterales, CRAB = carbapenem-resistant *Acinetobacter baumannii*, ARC = augmented renal clearance, TDM = therapeutic drug monitoring, LD = loading dose II = intermittent infusion, EI = extended infusion (3 to 4 h), CI = continuous infusion. All EI and CI require a LD, TBW = total body weight, * new refers to recently available BL/BLI combinations targeting specific resistance mechanisms.

Tabah, antibiotics, 2022

TDM « Therapeutique drug monitoring »

1. Dose de charge → d'autant plus si inflation hydrosodée
2. Adaptation à la fonction rénale (Insuffisance rénale - hyperclairance)
3. Connaissance sur la pharmaco-dynamie des antibiotiques: Temps/CMI , Pic/CMI ou AUC/CMI

- Pour mode administration: continue ou non; TDM +++
- Surtout pour minimiser la toxicité et augmenter la réponse aux ATB
- TDM disponible seulement pour certaines molécules
- Disponible en routine pour vancomycine, aminosides, de plus en plus pour les beta lactamines

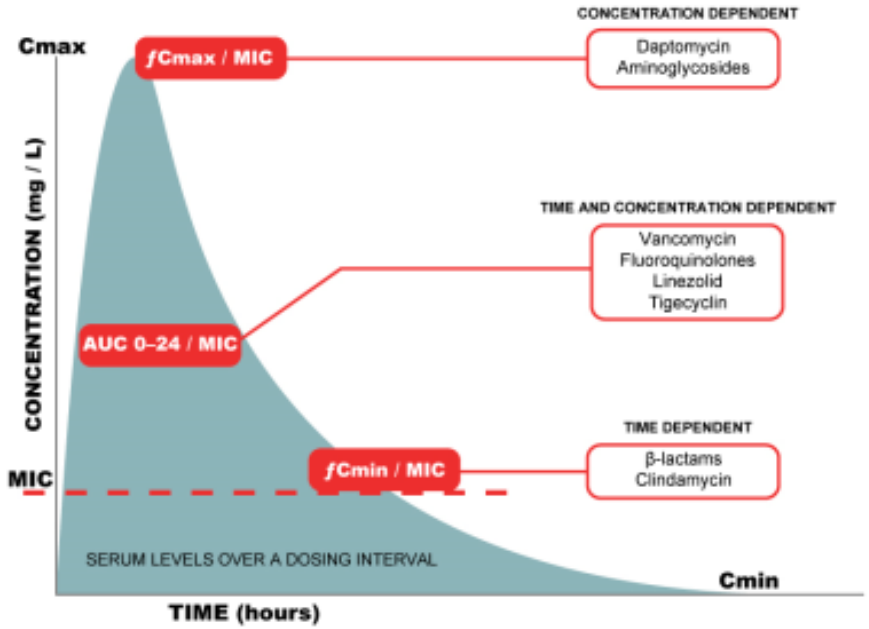
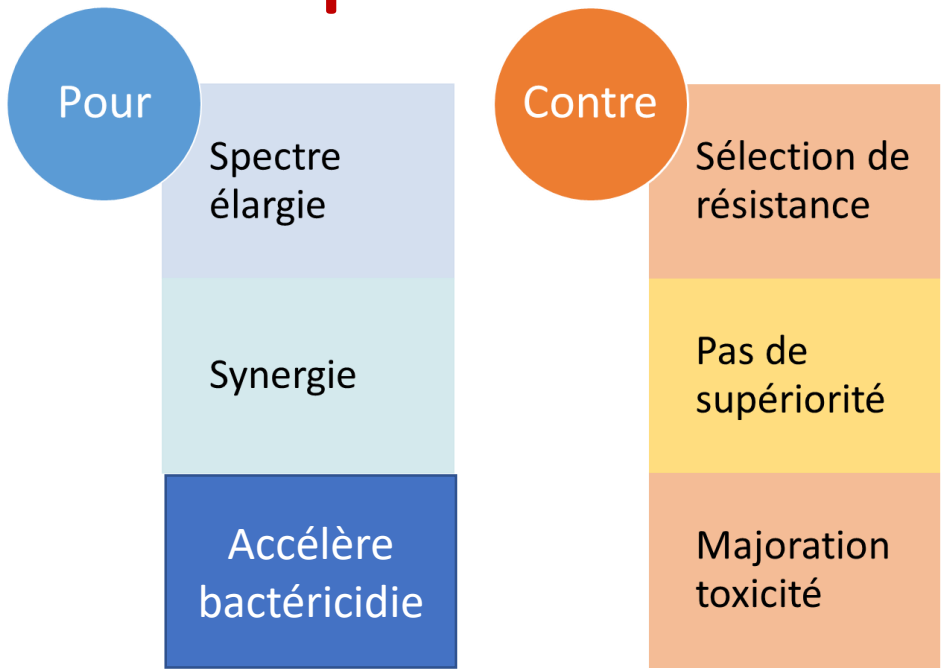


Figure 2. Pharmacokinetic targets for main antibiotic classes. Cmax = maximum serum concentration during a dosing interval, Cmin = trough (minimum) serum concentration over a dosing interval, MIC = minimum inhibitory concentration of the pathogen for the considered antibiotic, fCmax/MIC = ratio of free peak plasma concentration to MIC, fAUC/MIC = ratio of free unbound drug concentration area under the curve to MIC, fT > MIC = free unbound drug concentration time above the MIC.

Timsit, ICM, 2020; Tabah, antibiotics, 2022

Mono ou bithérapie pour les ICU-acquired BSI

- Souvent combinaison beta lactamine et aminoside ou fluoroquinolone
- Traitement possible en monothérapie pour les BSI à SAMS et à enterobacteries (AmpC hyperproductrice et ESBL)
- Controverse pour les acineto carba R, le pseudomonas, et les carba-PE
- Recommendation bithérapie pour les patients en choc septique, mais pas pour les sepsis sans défaillance hémodynamique



Recommendations

19. For adults with sepsis or septic shock and high risk for multidrug resistant (MDR) organisms, we **suggest** using two antimicrobials with gram-negative coverage for empiric treatment over one gram-negative agent
Weak recommendation, very low quality of evidence

20. For adults with sepsis or septic shock and low risk for MDR organisms, we **suggest against** using two Gram-negative agents for empiric treatment, as compared to one Gram-negative agent
Weak recommendation, very low quality of evidence

21. For adults with sepsis or septic shock, we **suggest against** using double gram-negative coverage once the causative pathogen and the susceptibilities are known
Weak recommendation, very low quality of evidence

Timsit, ICM, 2020; Evans, ICM, 2021

Stratégie de désescalade des antibiotiques

- Souvent à J2-J3 lors récuperation antibiogramme
- Réduire le nombre d'antibiotique et le spectre de l'antibiothérapie
- ! Quand la source peut être polymicrobienne comme dans les infections abdominales
- ! PK/PD.

Timsit, ICM, 2020

Durée de l'antibiothérapie

- Durée suffisante pour prévenir les rechutes et/ou récurrences
- !! durée trop longue expose effets adverses, toxicités, émergences de résistances, augmentation prix et des ressources
- J0= Contrôle de la source : traitement chirurgical et/ou négativation des hémocultures
- Clairance de la bactériémie: au moins une culture négative, après J2-J4 de l'infection
- Faire des hémocultures quotidiennes
- Durée de traitement codifiée en fonction du germe, de la source de l'infection, du bilan d'extension
- Toujours réévaluer entre J5 et J7 que l'infection soit contrôlé (Fièvre, syndrome inflammatoire, PN, CRP, PCT, défaillance d'organe, choc, négativation des hémocultures)
- Répéter les imageries, place de la scintigraphie aux leucocytes marqués, et PET Scanner

Timsit, ICM, 2020

En cas d'aggravation

- Non contrôle de la source de l'infection (abcès, matériel étranger, tissus infecté, endocardite, sous dosage ATB, acquisition de résistance, nouveau germe)
- Autre infection nosocomiale (KT, PAVM, Urines)
- → Refaire bilan infectieux complet
- → Timing modification ATB, contrôle de la source en fonction aggravation (choc?)
- En cas de fièvre sans aggravation clinique penser aux fièvres non infectieuses: allergie, TVP

Timsit, ICM, 2020

Durée antibiothérapie

Type d'infection	Durée ATB
Bactériémie sans complication à distance à SCN*	3-5 jours
Bactériémie sans complication à distance à BGN*	7 jours
Bactériémie sans complication à distance à streptocoque ou entérocoque*	7 jours
Bactériémie sans complications à distance à Staph Aureus§ ou candidémie*	14 jours
Thrombophlébite septique et endocardites	4 à 6 semaines
Bactériémie et complications à distance**	4 à 6 semaines
Arthrites	4 à 6 semaines
Ostéo-arthrites; Spondilodiscites	6 à 12 semaines
Abcès cérébrale	6 à 12 semaines
Bactériémies d'origine urinaire	Idem infection urinaire

- Liste non exhaustive

*comprend les infections de cathéters après ablation du cathéters et sans complication à distance

**corps étrangers, métastases septiques, micro-abcès

§ Staphylococcus lugdunensis idem que Staphylococcus aureus

- Rôle imagerie et évolution clinique-biologique pour guider durée

Gauzit, SPILF

Raccourcissement de la durée de l'antibiothérapie?

Pour

- Pas de comorbidités
- Source contrôlée
- CMI basse, bactéricidie
- ATB adapté dès le début
- Bonne diffusion
- Pas de matériel étranger
- Évolution clinique rapide

Contre

- Immunosuppression
- Pas de contrôle de la source
- BMR ou XDR
- Faible bactéricidie
- Mauvaise diffusion
- Matériel étranger
- Évolution lente ou défavorable

Les points clés

- SCN= la bactérie la plus fréquente/ savoir apprécier son rôle pathogène ou contaminant
- Contrôle de la source primordiale - drainer/débrider toute collection ou atteinte tissulaire
- L'antibiothérapie:
  - IV en optimisant la bactéricidie
  - L'association d'AB à justifier (élargir le spectre , accélérer la bactéricidie)
- La recherche localisations associées et porte d'entrée systématique, mais négative dans 15 à 25% des cas
- Durée de traitement
  - En fonction des caractéristiques de la bactériémie, du bilan d'extension, de l'évolution

Merci de votre attention

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Bloodstream infections in critically ill patients with COVID-19

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[illegible]: Little is known about the incidence and risk of intensive care unit (ICU)-acquired bloodstream infections (BSI) in critically ill patients with coronavirus disease 2019 (COVID-19).

Materials and methods: This retrospective, single-centre study was conducted in Northern Italy. The primary study objectives were as follows: (a) to assess the incidence rate of ICU-acquired BSI and (b) to assess the cumulative risk of developing ICU-acquired BSI.

Results: Overall, 78 critically ill patients with COVID-19 were included in the study. Forty-five episodes of ICU-acquired BSI were registered in 31 patients, with an incidence rate of 47 episodes (95% confidence interval [CI] 35-63) per 1000 patient-days at risk. The estimated cumulative risk of developing at least one BSI episode was of almost 25% after 15 days at risk and possibly surpassing 50% after 30 days at risk. In multivariable analysis, anti-inflammatory treatment was independently associated with the development of BSI (cause-specific hazard ratio [csHR] 1.07 with 95% CI 0.38-3.04 for tocilizumab, csHR 3.95 with 95% CI 1.20-13.03 for methylprednisolone and csHR 10.69 with 95% CI 2.71-42.17 for methylprednisolone plus tocilizumab, with no anti-inflammatory treatment as the reference group; overall *P* for the dummy variable = 0.003).

Conclusions: The incidence rate of BSI was high, and the cumulative risk of developing BSI increased with ICU stay. Further study will clarify if the increased risk of BSI we detected in COVID-19 patients treated with anti-inflammatory drugs is outweighed by the benefits of reducing any possible pro-inflammatory dysregulation induced by SARS-CoV-2.

KEYWORDS

BSI, coronavirus, COVID-19, SARS-CoV-2, steroid, tocilizumab

antibiotics

MDPI

Review

Use of Antimicrobials for Bloodstream Infections in the Intensive Care Unit, a Clinically Oriented Review

Alexis Tabah [1,2,3,*], Jeffrey Lipman [3,4,5], François Barbier [6], Niccolò Buetti [7,8], Jean-François Timsit [7,9] and on behalf of the ESCMID Study Group for Infections in Critically Ill Patients—ESGCIP [†]

(HA-

2. Either secondary to a source of infection or primary, when there is no identified source [2].
3. Complicated or uncomplicated, which was recently defined as a having definite source (among urinary, catheter, intra-abdominal, pneumonia, skin or soft tissues), and effective source control, in a non-immunocompromised patient, and with clinical improvement after 72 h of antimicrobial therapy (at least defervescence and haemodynamic stability) [3].
4. By clinical severity, which is the absence or presence of organ failures and the need for organ supportive therapy in the ICU.

- Antimicrobial therapy
  - The Importance of Getting It Right from the Start

  - Kumar and colleagues described in 2006 a 12% increase in crude mortality for each hour of delay to administer antimicrobials from the onset of hypotension and septic shock [10]. The above-mentioned study by Adrie and colleagues shows a 30% increase in mortality when no adequate treatment is given in the first 24 h [8]. In the evaluation of a multifaceted intervention to decrease sepsis mortality in a group of 40 German hospitals, Bloos and colleagues report an increase in the risk of death of patients with sepsis or septic shock of 2% for each hour of delay of antimicrobial therapy and 1% for each hour of delay in source control [11]
    Hranjec and colleagues i
    e conservative period, immediate antibiotic therapy was recommended for patients with shock.
    While controversy remains
    and these data present all the biases inherent to observational studies, they highlight how important it is that patients with BSIs receive early appropriate antimicrobial therapy

- 2.1.2. Broad-Spectrum Antibiotics and Combination Therapy?

  When the source is known, antibiotics should be targeted at the most common pathogens for the source as detailed in Table 1. Molecule choice takes into account risk factors for multidrug-resistant (MDR) or specific pathogens for the patient, according to their history and setting as shown in Table 2. For hospital-acquired infections, knowledge of colonisation from previous clinical or surveillance cultures is a valuable tool to optimise this choice [15,16].

  Combination therapy can provide very broad empirical coverage for different classes of pathogens by adding anti-MRSA and antifungal agents or molecules targeted at MDR Gram-negative bacteria (GNB). These should be used with parsimony, in patients with significant risk factors, and only as part of the empirical regimen with a plan to subsequently de-escalate all drugs that are not required [17,18].

- 2.1.3. The Importance of Sending Blood Cultures before Starting Antimicrobials

  2.1.4. The Advent of Molecular Rapid Diagnostic Testing

  as matrix-assisted laser desorption/ionisation–time of flight (MALDI-TOF) mass spectrometry [23]. Integrated solutions such as the Accelerate Pheno system automate both the identification and AST, providing accurate results in 90 min and 7 h, respectively. In a multicentre study, comparing with conventional BC processing, it accurately identified 14 common bacterial pathogens and 2 *Candida* sp. with sensitivities ranging from 94.6% to 100% [24]. The performance of AST results for methicillin-resistant *Staphylococcus aureus* (MRSA) and *Staphylococcus* sp. had an agreement of 97% with conventional processing. For GNB, the agreement on a panel of 15 antimicrobials was 94%, making this system suitable for prime clinical use [24].
  Colorimetric assays are relatively inexpensive and extremely accurate benchtop solutions to detect extended-spectrum beta-lactamase-producing (ESBL-Es) or carbapenemaseproducing

  Enterobacterales (CPEs) [21,25].

REDUIRE SPEDCTRE ATB

- Etended-Spectrum *b*-Lactamase-Producing Enterobacterales

- The MERINO trial randomised 391 patients with a BSIs due to ceftriaxone-resistant *Escherichia coli* or *Klebsiella pneumoniae* to piperacillin–tazobactam or meropenem [32]. Mortality was 12.3% for piperacillin–tazobactam compared with 3.7% for meropenem, rejecting non-inferiority and not supporting the use of piperacillin–tazobactam in severe infections due to ESBL-Es. Alternatives for cases where a carbapenem cannot be used include fluoroquinolones and trimethoprim-sulphamethoxazole. Those are especially interesting for BSIs with a urinary source as they concentrate in the urine [30]. While ceftolozane–tazobactam and ceftazidime–avibactam (CAZ-AVI) are potential alternatives, their use should be restricted as reserve antibiotics for those pathogens that cannot be treated otherwise

- we should avoid using piperacillin–tazobactam in patients with severe infections due to pathogens with inducible AmpC [36,37]. Cefepime is a good treatment choice as it is a weak inducer, and it is relatively stable against AmpC β-lactamases. Caution is warranted in pathogens with a MIC ≥ 4 µg/mL for cefepime as they may harbour an ESBL, making them prone to treatment failure. All carbapenems are stable and recommended for the

Epidemiology of ICU-Onset Bloodstream Infection: Prevalence, Pathogens, and Risk Factors Among 150,948 ICU Patients at 85 U.S. Hospitals*

Aurelie Gouel-Cheron, MD, PhD[1,2,3,4]

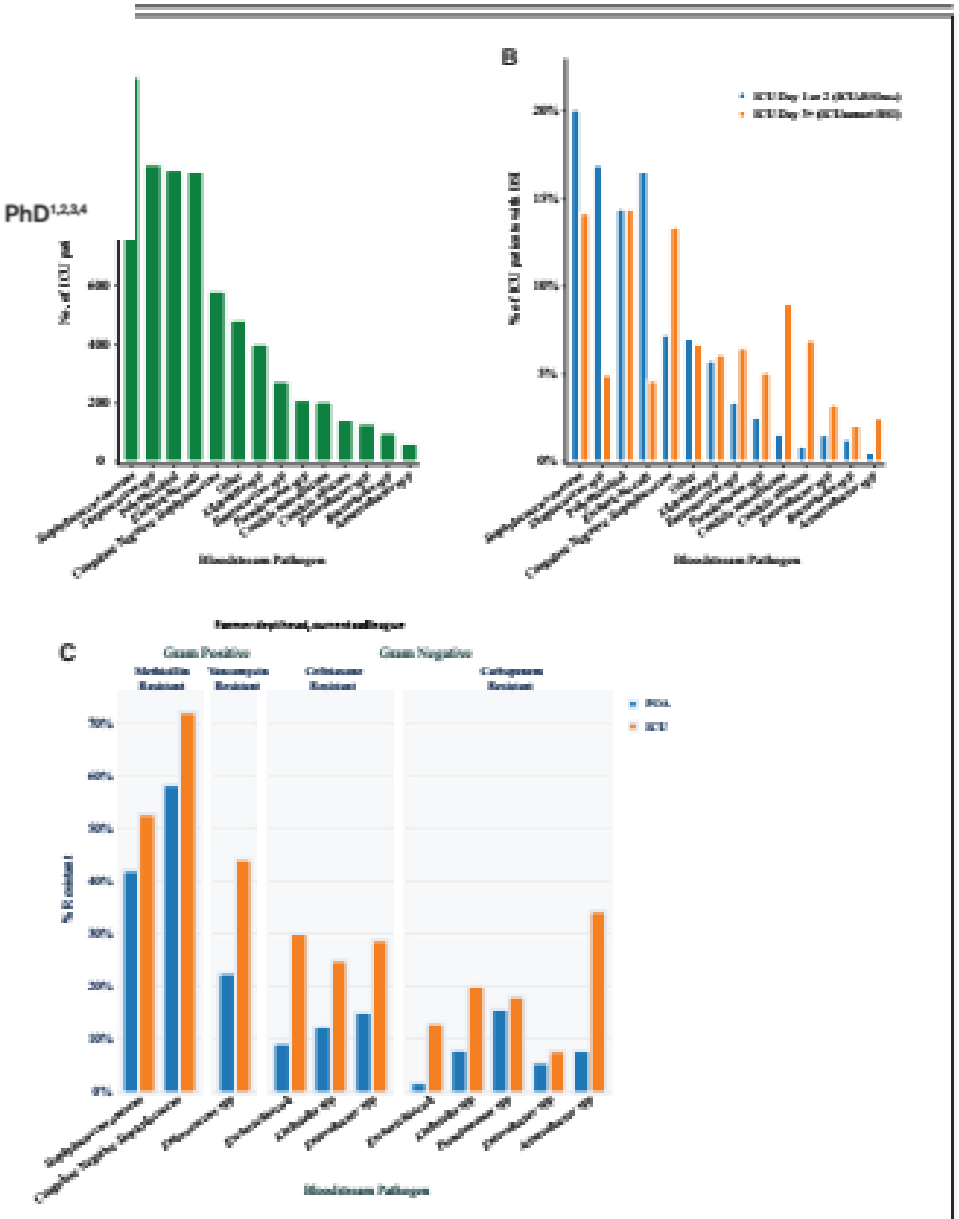
OBJECTIVES: Bloodstream infections (BSIs) acquired in the ICU represent a detrimental yet potentially preventable condition. We determined the prevalence of BSI acquired in the ICU (ICU-onset BSI), pathogen profile, and associated risk factors.

DESIGN: Retrospective cohort study.

DATA SOURCES: Eighty-five U.S. hospitals in the Cerner Healthfacts Database.

PATIENT SELECTION: Adult hospitalizations between January 2009 and December 2015 including a (≥ 3 d) ICU stay.

DATA EXTRACTION AND DATA SYNTHESIS: Prevalence of ICU-onset BSI (between ICU Day 3 and ICU discharge) and associated pathogen and antibiotic resistance distributions were compared with BSI present on (ICU) admission ($ICU\text{-}BSI_{POA}$); and BSI present on ICU admission day or Day 2. Cox models identified risk factors for ICU-onset BSI among host, care setting, and treatment-related factors. Among 150,948 ICU patients, 5,600 (3.7%) had $ICU\text{-}BSI_{POA}$ and 1,306 (0.9%) had ICU-onset BSI. Of those with $ICU\text{-}BSI_{POA,}$ 4,359 (77.8%) were admitted to ICU at hospital admission day. Patients with ICU-onset BSI (vs $ICU\text{-}BSI_{POA}$) displayed higher crude mortality of 37.9% (vs 20.4%) ($p < 0.001$) and longer median (interquartile range) length of stay of 13 days (8–23 d) (vs 5 d [3–8 d]) ($p < 0.001$) (considering all ICU stay). Compared with $ICU\text{-}BSI_{POA}$, ICU-onset BSI displayed more *Pseudomonas*, *Acinetobacter*, *Enterococcus*, *Candida*, and Coagulase-negative *Staphylococcus* species, and more methicillin-



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Narrative review

How do I manage a patient with enterococcal bacteraemia?

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Table 1
Diagnostic work-up and bases of enterococcal bacteraemia management according to the focus of infection

Main foci of infection	Rate [11]			Risk of IE	Echocardiography	Source control	Additional diagnostic procedures	Antibiotic therapy	Duration of therapy
	All (%)	*E. faecalis* (%)	*E. faecium* (%)						
Primary	22	23	20	High	Strongly recommended	—	Echocardiography ± US, CT, MRI, PET-CT, etc.	Combination	2–6 weeks depending on result of echocardiography
Endovascular devices[a]	15	17	10	Moderate	Recommended	Recommended	Venous doppler US of catheter exit-site to rule out infected thrombosis	Monotherapy	2–4 weeks depending on result of doppler US[c]
Abdominal tract	41	30	61	Low	Recommended	Recommended	Abdominal imaging to rule out intra-abdominal abscesses/ collection an need for source control	Broader spectrum[b]	1–2 weeks
Genitourinary tract	27	36	9	Low	Recommended	Recommended in case of catheter-associated infection	Urinary ultrasound to rule out complicated UTI	Monotherapy	1–2 weeks
Skin and soft tissue	5	5	6	Low	Recommended	Recommended		Monotherapy	1–2 weeks

[a] CVC (included haemodialysis catheters)/PICC/midline.
[b] High-risk of polymicrobial infections.
[c] To be extended to 4–6 weeks in case of endocarditis at echo.

Table 4
Summary of recommendations for the antibiotic treatment of enterococcal bacteraemia and endocarditis

	E. faecalis	Vancomycin-susceptible *E. faecium*	Vancomycin-resistant *E. faecium*
Uncomplicated bacteraemia	**Ampicillin** Alternative: • Piperacillin • Imipenem • Vancomycin • Daptomycin • Linezolid	**Vancomycin** Alternative: • Daptomycin • Linezolid	**Linezolid or Daptomycin** Alternative/rescue: • Daptomycin + β-lactams[a] • Teicoplanin
Endocarditis	**Ampicillin + ceftriaxone or ampicillin/penicillin + gentamicin** Alternatives: • Vancomycin + Gentamicin • Teicoplanin • Daptomycin + β-lactams[a]	**Vancomycin + gentamicin** Alternative: • Daptomycin + gentamicin • Linezolid • Daptomycin + β-lactams[a]	**Daptomycin or linezolid**. Consider adding a second synergistic antibiotic (gentamicin or beta-lactams)[a]

Dosages for the recommended antibiotics (all doses should be adjusted by kidney function):
Ampicillin: 1–2 g IV every 4 to 6 hours.
Piperacillin: 4 g IV every 8 hours.
Imipenem: 15–25 mg/kg IV every 6 hours.
Vancomycin: 25–30 mg/kg IV loading dose followed by 15 mg/kg every 8 hours.
Daptomycin: 6–8 mg/kg IV daily for uncomplicated non-vancomycin resistant enterococcal bacteraemia. At least 9 mg/kg IV daily for vancomycin-resistant enterococci.
Linezolid: 600 mg IV every 12 hours.
Ceftriaxone: 2 g IV every 12 hours.
Aqueous penicillin G sodium: 18–30 million U/24 h IV either continuously or in 6 equally divided doses.
Gentamicin: 3 mg/kg ideal body weight in 2–3 equally divided doses.
Teicoplanin: 6mg/kg IV (based on actual body weight), maximum 400mg every 12 hours for 3 doses loading dose followed by 6mg/kg (max 600mg) once daily.
[a] Evidence limited to short series, case reports or experimental studies.

Box 1
Summary of main recommendations for the management of enterococcal bacteraemia

Enterococcal bacteraemia should be suspected if

a patient presents a clinical picture of sepsis or worsening general clinical condition in association with - advanced age and/or hospitalization and/or immunosuppression

- Nosocomial infection under broad-spectrum antibiotics
- Prior enterococcal infections or colonization
- Comorbidities, in particular related to urogenital and intra-abdominal organs, and neoplasms (both solid and haematological)
- Recent surgery, mainly urinary or gastro-intestinal tract procedures (including hepato-biliary structures)
- Intravascular devices and/or indwelling urinary catheters

The initial work-up should include

- Physical examination to identify potential sources of bacteraemia (catheter-related phlebitis, murmurs, indwelling urinary catheters, biliary tract, surgical wounds, etc.) or related complications such as emboli, abscesses or osteomyelitis
- Blood cultures obtained before initiating antibiotic treatment (at least 2 sets; 3 sets separated by 30—60 min each in case IE is suspected[a])
- If available, use rapid identification methods for blood samples (e.g. MALDI-TOF)
- Perform antibiotic susceptibility tests tailored according to the enterococcal species and the local epidemiology. Usually, at least the following should be included: ampicillin, gentamicin, vancomycin, linezolid and daptomycin[b]
- Other cultures: catheter tips, urine, biliary fluid, peritoneal liquid, abscesses, deep surgical wound swab
- Potential additional studies: genitourinary and hepatobiliary ultrasound, abdominal CT scan, muscle-skeletal MRI, colonoscopy, ^{18}FDG-PET scan

Echocardiography in *E. faecalis* bacteraemia should be

- Always performed in stroke related to bacteraemia or relapse of bacteraemia
- Awaited if none of the risk factors below are present
- Considered if $\geq$ 1 of the risk factors below are present
- Performed if $\geq$ 3 of the risk factors below are present

Risk factors associated with endocarditis:
$\geq$2 positive BCs with *E. faecalis*
prosthetic heart valve, known native valve disease or prior IE
unknown origin of infection
community-acquired infection
murmur on auscultation
monomicrobial bacteraemia
duration of symptoms >1 week

Echocardiography in *E. faecium* and other EB except *E. faecalis* should be

restricted to cases with high clinical suspicion of IE such as relapse bacteraemia, signs of heart failure due to valve destruction and embolic events

Empiric therapy

- Ampicillin monotherapy can be used if there is not initial suspicion of complicated EB
- In the case of β-lactam allergy, vancomycin (if the local prevalence of VRE is low) is indicated. Daptomycin and linezolid are also good options, particularly in case of renal function impairment and high local rates of VRE
- When there is either a history of prior colonization or high local rates of *E. faecium*, empiric therapy should include vancomycin, daptomycin or linezolid
- If complicated EB is suspected, combined therapy and high doses are generally recommended. Particularly in the case of IE, ampicillin plus ceftriaxone or ampicillin plus gentamicin are the preferred options especially in community-acquired infections, which are mostly caused by *E. faecalis*. If *E. faecium* IE is suspected, vancomycin plus gentamicin is recommended until susceptibility to ampicillin is known

Length of directed therapy[c]

- The length of therapy of non-complicated EB ranges from 7 to 14 days. In case of VRE or multidrug-resistant strains, it could be extended to 14 days after blood cultures clearance
- For complicated EB other than IE, the usual length of therapy is 4 weeks. However, some cases may need longer courses
- For *E. faecalis* IE, the preferred options are ampicillin plus ceftriaxone (6 weeks; first option in case of HLAR) or ampicillin plus gentamicin (4 weeks in native valve IE and 6 weeks in prosthetic valve IE; a short regimen of 2 weeks of gentamicin might be used).

EB, enterococcal bacteraemia; IE, infective endocarditis; HLAR, high-level aminoglycoside resistance; VRE, vancomycin-resistant enterococci.
[a]Infective endocarditis or complicated bloodstream infection should be suspected if one or more of the following conditions are fulfilled: community-acquired EB, presence of indwelling intracardiac or intravascular devices (prosthetic valves including transcatheter inserted valves, cardiovascular implantable electronic devices, vascular grafts), persistent bacteraemia (positive blood cultures in spite of appropriate antibiotic treatment after 5 days), clinical manifestations or imaging findings suggestive of emboli, and new onset of cardiac murmur or heart failure.
[b]E-test is the cornerstone for treatment decision-making. Remarkably, in complicated *E. faecium* bacteraemia, performing a daptomycin e-test is advisable as the published breakpoint is likely is to be high, and it might also serve to guide daptomycin dosage.
[c]For the specific drugs recommended in EB and enterococcal IE treatment refer to Table 4.