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Enterococci, *Clostridium difficile* and ESBL-producing bacteria: epidemiology, clinical impact and prevention in ICU patients

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Summary

Most hospital-acquired infections arise from colonising bacteria. Intensive care patients and immunocompromised individuals are at highest risk for microbial invasion and subsequent infection due to multiple invasive procedures in addition to frequent application of chemotherapeutics and presence of poor microperfusion leading to mucosal disruption. In this narrative review, we summarise the literature on bacterial colonisation in intensive care patients, in particular the epidemiology, the clinical impact and respective infection control strategies of three pathogens, i.e., *Enterococcus* spp., extended-spectrum ß-lactamase producing gram-negative bacteria and *Clostridium difficile*, which have evolved from commensals to a public health concern today.

Key words: *Clostridium difficile; colonisation; enterococcus; enterobacteriaceae; ESBL; infection; intensive care unit; multidrug-resistant; outcome; VRE*

Introduction

Infections are the leading cause of death in intensive care units (ICUs) worldwide and mortality in infected ICU patients is more than twice as high compared to non-infected patients [1, 2]. Despite significant advances in intensive care therapy and infection prevention, incidence of nosocomial infections in ICU patients has remained high [1, 3]. The bacteria causing most hospital-acquired infections are staphylococci including methicillin-resistant *S. aureus* (MRSA), enterococci including vancomycin-resistant enterococci (VRE), *Candida* spp., *Clostridium difficile* and different often multidrug-resistant gram-negative bacteria [1].

Abbreviations

ARE ampicillin-resistant enterococci
CI confidence interval
ESBL extended-spectrum ß-lactamase
ESBL-GNB extended-spectrum ß-lactamase producing gram-negative bacteria
ICU intensive care unit
MRSA methicillin-resistant *Staphylococcus aureus*
OR odds ratio
VRE vancomycin-resistant enterococci

In healthy individuals, an ecological community of commensals, symbiotes and pathogens – the microbiome – is in equilibrium with the host. If anatomical barriers or host defenses are disrupted, invasion of colonising bacteria and subsequent infection can arise [4].

In ICU patients, multiple invasive procedures (e.g., central venous catheters) and the presence of poor microperfusion lead to integrity loss of skin and mucosae with risk of invasive infection [5]. Furthermore, ICU patients are per se immunocompromised due to the severity of the disease [6]. Selected by pressure of antibiotic treatments, colonising multidrug-resistant bacteria can outgrow commensals from the microbiome [7] and become invasive. In view of the global rise of infections with multidrug-resistant bacteria and a concomitant lean development pipeline for antimicrobial agents, the "Infectious Diseases Society of America" stated that we should consequently maximise infection control strategies [8].

In this narrative review, we summarise the literature on bacterial colonisation in ICU patients, in particular the epidemiology, the clinical impact and respective infection control strategies focusing on three intestinal bacteria, i.e. *Enterococcus* spp., extended-spectrum ß-lactamase producing gram-negative bacteria (ESBL-GNB) and *Clostridium difficile*.

Methods

We searched PubMed/MEDLINE in November 2013, without restrictions, using the following search strategy with Boolean operators: "("enterococcus" OR "enterococci" OR "VRE" OR "ARE" OR "ESBL" OR "*Clostridium difficile*" OR "*C. difficile*") AND ("intensive care unit" OR "ICU")". In addition, we searched the references of cited articles in this review for other appropriate studies.

Only articles focusing on adult populations (≥18 years) written in English, German, French or Italian language were included. Several other search terms were applied to identify appropriate studies regarding specific questions

considered in this narrative review (e.g., to describe the global epidemiology of enterococci).

Enterococci

Background

E. faecalis and *E. faecium* – the species most frequently encountered in clinical isolates [9] – have evolved from intestinal commensals to the third highest ranking cause of nosocomial infections in the United States [10]. Enterococci are characterised by a remarkable genomic flexibility [11] with the ability to incorporate foreign mobile genetic elements carrying e.g., resistance genes to multiple antibiotics in addition to chromosomal resistance genes [12, 13]. The increasing rate of antimicrobial resistance in enterococci, e.g. to ampicillin or vancomycin, are of major clinical importance [14, 15]. Since the first description of VRE in a clinical isolate in Europe in 1988 [16], VRE are increasing in prevalence worldwide, capable of spreading vancomycin resistance genes (mainly *vanA* and *vanB*) via transposons to vancomycin-susceptible enterococci and rarely to other bacteria (e.g., MRSA) [17, 18]. *VanA* is widely prevalent in the United States and Korea, whereas *vanB* has been introduced as main genotype in VRE epidemics in Australia and Singapore [19]. Chromosomal vancomycin resistance genes are less transmissible (e.g., *vanC*) and are related to the use of the animal growth promoter avoparcin in Europe until 1997 and rarely cause infection [20, 21].

Whereas in the Unites States VRE nowadays dominate the epidemiology of nosocomial enterococcal infections, the situation in Europe is more diverse: Germany, Greece, England, Ireland and Portugal have high VRE rates of >10%, whereas in most European countries an increase in ampicillin-resistant enterococci (ARE) is observed since the year 2000 [22, 23]. According to the European Center for Disease Prevention and Control (ECDC) report 2012, overall ampicillin-susceptibility rates of *E. faecalis* isolates were >75% in all European countries (mostly >95%) compared to <50% in *E. faecium* (range 0.8–33.3%) [22].

Clinical impact of infection and colonisation with enterococci in ICU patients

According the Unites States "National Healthcare Safety Network" 2006–7, enterococci accounted for 12.1% of hospital-acquired infections in ICU patients (16.0% of central-line-associated bloodstream infections and 14.9% of catheter-associated urinary tract infections) [10]. In a global ICU point-prevalence study from 2007, VRE rates among enterococcal clinical isolates differed widely in the geographic regions of the world: Western Europe 31.1%, Eastern Europe 31.4%, Central/South America 46.9%, North America 47.8%, Oceania 52.6%, and Asia 37.0% [1].

In hospitalised patients, densities of ampicillin-resistant *E. faecium* colonisation in stool increases 10–fold compared to *E. faecalis*, leading to overgrowth [24] and possibly facilitated invasive infection. Table 1 gives an overview of the published VRE and ARE colonisation and infection rates in ICU patients. On admission, VRE colonisation rates range from 0.6% [25] to 42.6% [26]. VRE acquisition rates during hospitalisation range from 1.2% [25] to 41.4% [27]. Major risk factors for VRE colonisation/infection are length of hospital stay [28–35], high VRE colonisation pressure (high rate of colonised patients on the same ward) [28, 36, 37], and antimicrobial therapy with broad-spectrum antibiotics [25, 27, 30, 32, 33, 35–44]. To note, not only antimicrobial therapy with vancomycin [27, 30, 32, 37, 38, 40, 41, 44, 45] but also metronidazole [30, 33, 38], quinolones [30, 36, 38, 44], cephalosporins [27, 30, 33, 36, 37, 39], carbapenems [25, 36, 40, 44], and other broad-spectrum antibiotic classes were associated with VRE in ICU patients.

In contrast to VRE, only few studies focused on ARE colonisation in ICU patients [46–50]. In two prospective studies from the Unites States, ARE were found in 5.0% and 5.4% of patients admitted to a general ward or ICU, and acquisition during hospitalisation in 18.9% [49, 50]. In a Dutch ICU, ARE were present on admission screening in 28% of patients; new ARE clones were acquired during hospitalisation in 83% [46]. Documented risk factors for ARE colonisation are previous hospitalisation [49], prior antimicrobial therapy [49, 50], enteral tube feeding [49], urinary bladder catheter [50], and total nursing care [50].

The relative contribution of both cross-transmission and selection under antibiotic pressure to the burden of VRE/ARE colonisation is largely unknown. Typing methods such as multilocus sequence typing have allowed identification of nosocomial *E. faecium* clones, such as clonal-complex 17 [51], which contain genes conferring virulence and resistance to multiple antibiotics. Several studies have demonstrated the importance of cross-transmission and environmental contamination of VRE [27, 28, 30, 36, 37, 52–54] and ARE [50, 55] estimating cross-transmission as the cause of VRE colonisation in up to 85% [27].

Once colonised with VRE/ARE, ICU patients or haematological patients have the highest risk to develop an invasive infection [56]. In VRE-colonised ICU patients, infection rates of up to 45% [57] and bacteremia rates of up to 16% [32] have been reported [58]. In contrast, VRE infection prevalence among non-colonised ICU patients is negligible with <2% [58]. The prevalence of ARE infections in colonised ICU patients or other high-risk populations has not been described so far, but infected patients were colonised with the same ARE type in 100% of patients in a European study [46].

Colonised ICU patients developing an enterococcal infection are sicker, i.e. have more co-morbidities, higher disease severity scores on admission and have increased mortality rates compared to non-infected patients [1]. At highest risk are neutropenic patients with a VRE infection rate up to 27% once colonised [59] and a mortality rate up to 60% [60–62]. The question, whether this is due to virulence of VRE or an effect of the underlying condition is still a matter of debate [63–67]. Besides host factors, bacterial virulence and treatment might affect outcome. A meta-analysis including a total of 1,614 enterococcal bloodstream infections indicated that patients with VRE were more likely to die than those with vancomycin-susceptible enterococci (odds ratio (OR) 2.52; 95% confidence interval (CI) 1.9–3.4) [67].

Table 1: Studies on vancomycin- and ampicillin-resistant enterococci: rates and risk factors for colonisation/infection in adult patients (intensive care unit setting only).

Study design and reference	Study year	Country	Total of colonised patients	Rate of co-lonisation on admission[a], %	Rate of HA colonisation[a], %	Rate of infections, %	Risk factors for VRE/ARE colonisation and/or infection
Vancomycin-resistant enterococci							
ROS [38]	2013	Saudi Arabia	30	NA	NA	NA	Multiorgan failure, chronic renal failure, VAN, MN, P/T, QN, gastrointestinal contrast procedure
POS [39]	2012	Taiwan	97	5.8	5.4	10.6[b]	Septic shock, cardiovascular disease, endocrine disorder, 1st /2nd-gen. cephalosporin, antifungal agent
ROS [40]	2012	Brazil	78	15.0	9.9	NA	Diabetes mellitus, nephropathy, any antimicrobial therapy, VAN, CAR
POS [41]	2012	Korea	290	17.6	12.3	15.2[c]	Polymicrobial infection, haemodialysis catheter, intra-abdominal procedure, long duration of VAN therapy
ROS [45]	2012	Korea	153	3.4	NA	NA	Polymicrobial infection, haemodialysis catheter, intra-abdominal procedure, long duration of VAN therapy
ROS [36]	2011	United States	885	8.0	2.9	NA	Chronic renal failure, wounds, rash, surgery, surgical drain, intubation, central line catheter, low albumin, high VRE colonisation pressure, macrolide, QN, AG, 3rd-gen. CEPH, CAR
POS [42]	2011	United States	19	2.5	NA	NA	Any antimicrobial therapy, rehospitalisation, intravenous drug user, haemodialysis, immunocompromised status
ROS [28]	2009	Korea	52	6.1[d]	NA	NA	Female gender, GCS <8, co-morbidity, invasive catheters, long duration of mechanical ventilation, long hospital stay, presence of nearby VRE positive patient
POS [43]	2009	Korea	34	4.4	NA	NA	Infectious disease, rehospitalisation, any antimicrobial therapy
POS [208]	2008	United States	168	8.9	4.1	NA	Environmental VRE contamination, prior room occupant with VRE colonisation
POS [209]	2006	Italy	56	2.6	8.7	3.6	NA
POS [210]	2006	United States	309	9.7	7.5	NA	NA
POS [44]	2005	United States	312	12.8	NA	NA	Any antimicrobial therapy, liver disease, renal disease, VAN, IMI, QN
POS [29]	2005	Brazil	48	NA	32.6	NA	Long hospital stay, long duration of any antimicrobial therapy, rehospitalisation, nosocomial infection
POS [84]	2004	United States	136	10.0	NA	NA	NA
POS [211]	2004	Taiwan	816	8.0	10.8	1.1	NA
POS [25]	2003	Australia	66	0.6	1.2	0	Rehospitalisation, CAR, ticarcillin-clavulanate
ROS [30]	2003	United States	63	18.9	22.6	3.2[b]	Long hospital stay, acute respiratory failure, sepsis, multiorgan failure, central venous catheter, VAN, CEPH, MN, QN, location in high-risk room
POS [31]	2003	United States	201	24.5	21.0	NA	COPD, high APACHE score, sucralfate, *C. difficile* diarrhea, vasopressor, tracheostomy, long duration of mechanical ventilation, long hospital stay, chronic dialysis, rehospitalisation
POS [26]	2002	United States	26	42.6[e]	22.2[e]	NA	Rehospitalisation, enteral tube feeding
POS [57]	2001	Unites States	23	9.4[f]	11.3[f]	45.0	NA
POS [212]	2001	Argentina	1	0.7	NA	NA	NA
POS [213]	1999	United States	10	6.3	9.8	0	NA
POS [32]	1999	Israel	14	9.8	14.5	7.1	Young age, any antimicrobial therapy, long duration of any antimicrobial therapy, VAN, rehospitalisation, long hospital stay
POS [214]	1999	Australia	1	0.7	NA	NA	NA
POS [33]	1999	United States	46	12.1	14.1	NA	Gastrointestinal disease, prior solid organ transplantation, long hospital stay, rehospitalisation, high APACHE score, 2nd/3rd-gen. CEPH, MN
POS [34]	1999	United States	13	15.7[c]	NA	NA	Immunosuppression, neutropenia, long hospital stay
POS [35]	1998	Netherlands	98	14.3	18.3	NA	Long hospital stay, any antimicrobial therapy

POS [37]	1998	United States	45	NA	29.4	NA	High VRE colonisation pressure, VAN, 3rd-gen. CEPH, enteral tube feeding, sucralfate, high APACHE score
POS [27]	1996	United States	31	13.0[g]	41.4[g]	NA	Old age, 3rd-gen. CEPH, VAN
Ampicillin-resistant enterococci							
POS [46]	2012	Netherlands	21	27.6[d]	NA	NA	NA
POS [49]	1996	United States	19[h]	5.4	NA	NA	Rehospitalisation, treatment with >3 antibiotics, 3rd-gen. CEPH, enteral tube feeding
POS [50]	1992	United States	23[h]	5.0	18.9	NA	Any antimicrobial therapy, CEPH, urinary bladder catheter, need for total nursing care

Partly adapted from Ziakas et al. [58]. Interventional trials were excluded.
HA = hospital-acquired; VRE = vancomycin-resistant enterococci; NA = not assessed; ROS = retrospective observational study; POS = prospective observational study; VAN = vancomycin; AG = aminoglycoside; QN = quinolone; MN = metronidazole; CAR = carbapenem; P/T = piperacillin/tazobactam; CEPH = cephalosporin; IMI = imipenem; APACHE = acute physiology and chronic health evaluation; COPD = chronic obstructive pulmonary disease; GCS = Glasgow Coma Score; ICU = intensive care unit.
[a] Rectal/perirectal colonisation if not stated otherwise. HA colonisation was defined as negative culture within the first 48h of ICU admission and subsequent positive culture; [b] among patients with HA VRE colonisation; [c] among patients with VRE colonisation on admission; [d] total VRE colonization rate (on admission or HA); [e] based on rectal, faecal, and/or urine cultures; [f] based on rectal, faecal, respiratory, and/or urine cultures; [g] based on rectal, integumental (groin and arm), oropharyngeal, tracheal, and/or gastric cultures; [h] ICU and/or medical ward.

Extended-spectrum ß-Lactamase (ESBL) producing gram-negative bacteria

Background

One of the most important resistance mechanisms of gram-negative bacteria are ß-lactamases conferring resistance to ß-lactam antibiotics by hydrolisation of their ß-lactam-ring [68]. Of the many different ß-lactamases, ESBLs comprise the largest group of enzymes [68], causing resistance to newer ß-lactam antibiotics, including the third-generation cephalosporins and monobactams, but not the cephamycins and carbapenems [69, 70].

ESBLs were initially recognised in clinical bacterial isolates in the 1980's and are a rapidly increasing public health threat today [68, 71]. The different gene classes encoding ESBLs are located on plasmids or chromosomes. Plasmids encoding ESBLs easily spread among Enterobacteriaceae, mainly *Escherichia coli* and *Klebsiella pneumoniae* but also among non-fermentative gram-negative bacteria, such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii* [71]. A variety of distinct ESBL genotypes predominate in certain regions of the world (e.g., CTX-M-15 is becoming dominant in most European countries) [72–74].

Based on a recent surveillance trial, the rate of ESBL-producers among clinical *K. pneumoniae* isolates, was highest in Latin America (44.0%), followed by Asia/Pacific Rim (22.4%), Europe (13.3%), and North America (7.5%) [75]. The same geographical ranking order of ESBL producers was observed among *E. coli* isolates, although lower for all four regions (13.5%, 12.0%, 7.6%, and 2.2%, respectively) [75]. In Europe, 2012, resistance to third-generation cephalosporins ranged from 0% (Romania) to 74.8% (Bulgaria) and from 4.4% (Sweden) to 38.1% (Bulgaria) for *K. pneumoniae* and *E. coli*, respectively [22].

In addition to ESBLs, the large plasmids commonly harbor genes encoding for resistance to other antibiotic classes [76] such as aminoglycosides (5.6–83.5%), tetracyclines (44.4–61.1%), trimethoprim-sulfamethoxazole (5.6–25.4%), and ciprofloxacin (22.2–44.2%) [77].

In a recent Swiss hospital-wide surveillance study of patients with any clinical ESBL-GNB isolate and no current ESBL-GNB specific antimicrobial therapy, urine samples were positive in 110 of 133 patients (82.7%), rectal swabs in 69.2%, skin swabs of the groin in 35.3%, and throat swabs in 12.8% [78].

Clinical impact of infection and colonisation with ESBL-GNB in ICU patients

Global surveillance data from a 1–day point prevalence study on 1,265 ICUs in 2007 showed an overall ESBL rate of 3.0% among clinical isolates of gram-negative bacteria (North America 0.4%, Western Europe 3.0%, Asia 4.5%) [1].

The published ESBL-GNB colonisation rates of ICU patients (table 2) range from 2.2% [79] to 49.0% [80] with important geographical differences. The highest ESBL-GNB colonisation rates on ICU admission have been found in Korean [81] (42.5%), Indian [80] (49.0%), and Spanish [82] (38.3%) ICUs, whereas especially ICUs from the Unites States [79, 83, 84] and Belgium [85] exhibited low colonisation rates (2.2–6.2%).

The three main risk factors for colonisation/infection with ESBL-GNB in ICU patients are length of hospital stay [80, 86], high ESBL-GNB colonisation pressure [86, 87], and broad-spectrum antibiotics [79, 80, 82, 86–88] (table 2).

ESBL-GNB infection rates in colonised ICU patients range from 4.9% [87] to 68.8% [85]. The largest of these studies was a prospective 3.5–year single-centre study from the Unites States. Out of 5,209 ICU patients, 2.2% were rectally colonised with ESBL-producing *E. coli* or *Klebsiella* spp. on admission, and in 24.8% the same ESBL-GNB was found in a clinical sample thereafter [79]. In contrast, among the 5,092 patients not colonised with ESBL-GNB, only 0.6% had a subsequent positive clinical culture [79]. One of the few prospective studies on outcome of rectal ESBL-GNB colonisation was performed in 513 hospitalised haematological and oncological patients in Germany. Colonised patients had a risk ratio of 4.5 to develop a subsequent ESBL-GNB bloodstream infection (95% CI 2.9–7.0) [89]. A 10–year prospective French study including 710 liver transplant patients showed an even higher infection rate in patients with pre-transplant fecal ESBL-GNB colonisation (44.8%) compared to non-carriers (3.8%; p <0.0001), proven by identical PCR typing in 76.9%. Another study including 4 high-risk units (2 ICUs,

1 solid organ transplant unit, and 1 haematology/oncology unit) in the Unites States found an ESBL-GNB bloodstream infection rate of 8.5% (35/413) in colonised patients [90]. On the other hand, one study in patients with acute leukaemia or haematopoietic stem cell transplantation could not confirm an association between colonisation and infection with ESBL-producing *E. coli* or an increased in-hospital mortality (bloodstream infections rate with ESBL-producing *E. coli* in 1.5% of colonised vs 1% of non-colonised patients; p = 0.7) [91].

Several, mostly retrospective studies showed significantly longer length of hospital stay and higher mortality rates in patients with bloodstream infections due to ESBL-producing versus non-producing GNB [90, 92–98]. The increased mortality in bloodstream infections with ESBL-GNB is mainly caused by inadequate initial therapy and is likely not a consequence of higher bacterial virulence [99].

Clostridium difficile

Background

C. difficile is a gram-positive, anaerobic and spore-forming rod causing mainly antibiotic-associated diarrhea. Symptoms range from uncomplicated diarrhea to severe pseudomembranous colitis and toxic megacolon [100]. *C. difficile* is a public health concern worldwide representing the leading cause of hospital-associated infectious diarrhea [101]. Increases in incidence, morbidity, and recurrence rate have been reported in the United States, Canada, and Europe [102]. In contrast, little is known on the epidemiology of *C. difficile* infection in Asian countries [103].

The increased virulence of *C. difficile* has been attributed to the spread of fluoroquinolone-resistant ribotype 027 (RT027, BI/NAP01), which produces, in addition to toxins A and B, a binary toxin of unspecified significance [102, 104–106]. *C. difficile* RT027 is the cause of multiple healthcare-associated outbreaks in the United States, Canada, and Europe [107–109]. Furthermore, community-acquired *C. difficile* infection is increasing, with another hypervirulent ribotype (078), as the main culprit. Compared to North America and Europe, ribotype 017 and 018 have been shown to be the most prevalent types in Asian hospitals [103].

C. difficile is thought to be mainly transmitted via hands of healthcare workers and by the contaminated environment [110]. Hand hygiene with alcoholic solutions is not associated with a higher risk of transmission despite the fact that alcohol does not have any antimicrobial effect against *C. difficile* [111]. Healthcare workers could be asymptomatic intestinal *C. difficile* carriers acting as a reservoir for cross-transmission in the hospital. However, in a non-outbreak setting, intestinal colonisation of healthcare workers occurs at similar frequency as among healthy adults [112–115]. The

Table 2: Studies on extended-spectrum ß-lactamase producing gram-negative bacteria: rates and risk factors for colonisation/infection in adult patients (intensive care unit setting only).

Study design and reference	Study year	Country	Total of colonised patients	Rate of co-lonisation on admission[a], %	Rate of HA colonisation[a], %	Rate of infection, %	Risk factors for ESBL-GNB colonisation and/or infection
ROS [86]	2013	United States	267	NA	3.5[b]	NA	Rehospitalisation, long hospital stay, high ESBL-GNB colonisation pressure, malignancy, cerebrovascular disease, renal disease, P/T, CFM, antifungal agents, anti-pseudomonas ß-lactams, anti-MRSA therapy
POS [81]	2013	Korea	40	42.5[c]	NA	NA	NA
POS [87]	2012	France	110	15.4	13.2	4.9	Male gender, old age, severe sepsis/septic shock, high ESBL-GNB colonisation pressure, long broad-spectrum antibiotic therapy, penicillin/beta-lactamase inhibitor, QN, 3rd-gen. CEPH, long hospital stay, surgery within past year, hospital admission in another country, rehospitalisation, neurological disease, transfer from another ICU, urinary tract disease
POS [88]	2012	France	63	4.2	4.2	NA	ß-lactams and CAR
POS [80]	2010	India	47	49.0[c,d]	NA	NA	Long mechanical ventilation, long hospital stay, comorbidities, use of ≥3 antibiotic groupse
POS [79]	2007	United States	117	2.2	NA	24.8	Old age, high infectious disease-specific chronic disease score, VAN, P/T, CFM, IMI
POS [83]	2007	United States	97	4.1	1.3	NA	Horizontal transmission[f]
POS [85]	2006	Belgium	32	6.2	8.6	68.8	NA
POS [84]	2004	United States	32	2.3[g]	NA	31.2	NA
POS [82]	1997	Spain	72	38.3[c]	NA	NA	High clinical severity score at admission, arterial or urinary catheterisation, total parenteral nutrition, mechanical ventilation, antimicrobial therapy

Interventional trials were excluded.

HA = hospital-acquired; ESBL = extended-spectrum ß-lactamase; GNB = gram-negative bacteria; POS = prospective observational study; ROS = retrospective observational study; VAN = vancomyin; QN = quinolone; MN = metronidazole; CAR = carbapenem; P/T = piperacillin/tazobactam; CEPH = cephalosporin; CFM = cefepime; IMI = imipenem; ICU = intensive care unit; MRSA = methicillin-resistant *Staphylococcus aureus*; NA = not assessed.

[a] Rectal/perirectal colonisation if not stated otherwise. HA colonisation was defined as negative culture within the first 48h of ICU admission and subsequent positive culture; [b] HA colonisation and/or infection; [c] total VRE colonisation rate (on admission or HA); [d] based on cultures from the nares, oropharynx, and/or rectum; [e] other pathogens than ESBL-GNB included in analysis; [f] based on an ecological correlation; [g] colonisation within the first 72 hours after admission.

importance of nosocomial transmission of *C. difficile* has been questioned by a recent study from Oxfordshire, United Kingdom [116]. Using whole-genome sequencing, 45% of patients with *C. difficile* had genetically distinct strains compared to patients previously diagnosed with *C. difficile*. Noteworthy, even within a single patient, diverse subtypes were detected indicating different transmission events. These observations suggest that genetically diverse sources play a major role in *C. difficile* transmission [116].

Clinical impact of infection and colonisation with *Clostridium difficile* in ICU patients

C. difficile is found as a part of the normal intestinal flora in 1.0% [117] to 12.9% [114] of healthy individuals. Most studies analysing *C. difficile* colonisation in hospitalised patients have been performed on geriatric wards [118–121]. One study performed in ICU patients documented a colonisation rate of 34.6% [122].

Whether *C. difficile* colonisation is a risk for infection [123] or has a protective effect [124] is not clear yet. The published prevalence of *C. difficile* infection and corresponding mortality rate among ICU patients range from 0.5% [125] to 7.3% [126] and from 19.7% [127] to 36.7% [128], respectively (table 3). For ICU patients, *C. difficile* infection has not been associated with an increase in mortality [126, 128, 129]. The recurrence rates of *C. difficile* infection in ICU patients are highly variable as follow-up periods differ in most studies. Following treatment for *C. difficile*, recurrence rates in ICU patients can be as high as 12.7% [129].

Several risk factors for *C. difficile* infection and related mortality in ICU patients have been described (table 3). Antibiotic treatment is strongly associated with *C. difficile* infection (OR 6.67; 95% CI 1.76–25.31) [130] probably due to the fact that antibiotics interfere with intestinal colonisation resistance leading to overgrowth of *C. difficile* and toxin production, eventually causing infection [131]. Most classes of antibiotics have been associated with *C. difficile* infection in the hospital and community setting [132] with highest risks described for quinolones, cephalosporins, and clindamycin [133]. Other risk factors are older age, use of proton pump inhibitor and the presence of hypervirulent strains [130].

Infection control strategies

Background

Generally, infection control on ICUs includes a bundle of prevention strategies. Wenzel and Edmond suggested to

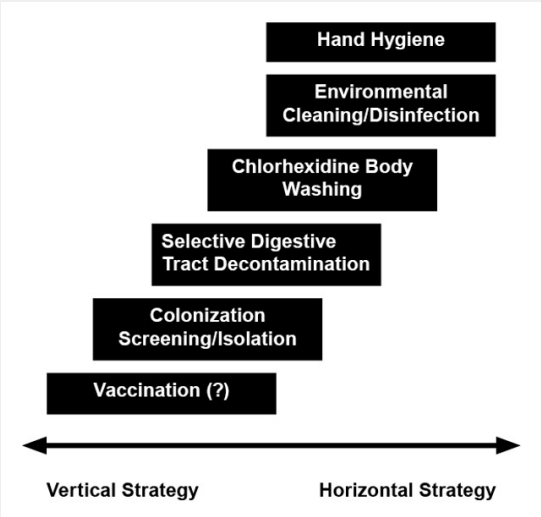

Figure 1

Infection control strategies in intensive care units: A continuum. Infection control in intensive care units can involve vertical and horizontal strategies [134, 135]. While vertical interventions aim to reduce colonisation and infection with a certain pathogen, horizontal interventions try to minimise the spread of pathogens in general by using a universal approach [134, 135]. For prevention of bacterial infection in ICU patients, vaccines may be of interest in the future.

Table 3: Studies on *Clostridium difficile*: infection rate, recurrence rate, mortality, and risk factors for infection/death in adult patients (intensive care unit setting only).

Study design and reference	Study year	Country	CDI rate, %	CDI recurrence rate, %	Mortality in CDI, %	Risk factors for CDI or CDI-associated mortality
ROS [129]	2013	United States	6.6	12.7	25.1[a]	Old age, long hospital stay, medical patients, high APACHE II score, end-stage renal-disease, end-stage liver disease, hospital ward-to-ICU transfer, vasopressors, vancomycin enema
ROS [125]	2011	United Kingdom	0.5	0.0	25.9[b]	NA
ROS [126]	2011	Unites States	7.3	NA	25.3[a]	Male sex, long hospital stay, high APACHE III score, prior room occupant with CDI
ROS [215]	2008	United Kingdom	1.5–4.8[c]	NA	33.9[a]	Old age, male sex, high APACHE II score
ROS [128]	2007	United States	NA	NA	36.7[d]	Old age, medical patients, high APACHE II score, malignancy, low serum albumin, septic shock, ward-to-ICU-transfer, colonic thickening on CT
ROS [216]	2007	United States	NA	NA	27.6[a]	Old age, renal failure, hepatic failure, high SOFA score, organ failure, septic shock, respiratory failure
ROS [127]	2007	United States	4.1	2.6	19.7[e]	Long hospital stay, enteral tube feeding, mechanical ventilation, *Pseudomonas aeruginosa* bacteremia, VRE colonisation or infection, gastric acid suppressive therapy, *C. difficile* colonisation pressure, antimicrobial therapy

CDI = *Clostridium difficile* infection; ROS = retrospective observational study; APACHE = acute physiology and chronic health evaluation; ICU = intensive care unit; NA = not assessed; CT = computed tomography; SOFA = sequential organ failure assessment; VRE = vancomycin-resistant enterococci.
[a] in-hospital mortality rate; [b] 30–day in-hospital mortality rate; [c] 3 consecutive surveillance periods; [d] crude 30–day mortality rate; [e] mortality rate during ICU stay.

stratify such bundles in vertical and horizontal strategies (fig. 1), although considerable overlap between the two approaches exists [134, 135]. Vertical strategies include all pathogen-specific modules to reduce colonisation and/or infection (e.g., selective decolonisation in MRSA carriers). In contrast, horizontal interventions focus on minimising the spread of all pathogens between patients by using universal approaches (e.g., hand hygiene, chlorhexidine body washing) [134, 136].

Hand hygiene as an essential part of infection control is highly effective in reducing all sorts of hospital-acquired infections [137] and therefore is recommended for the prevention of infections caused by VRE, ESBL-GNB and *C. difficile* [138–141].

A limitation of infection control studies is the fact that results from a study performed in a specific epidemiological context may not apply to other epidemiological settings. Furthermore, steadily evolving and changing antimicrobial resistance patterns make it difficult to draw long-term conclusions.

Colonisation screening and contact precautions (vertical strategy)

Screening for nosocomial pathogens in asymptomatic carriers aims to early identify colonised patients and to timely apply appropriate isolation precautions to prevent spread in the hospital. Interventions in patients with a positive screening result are e.g., contact isolation and decolonisation [142]. A challenge is selection of patients at risk – ranging from targeted screening of high-risk patients (e.g., haematopoietic stem cell recipients, ICU patients) to universal screening performed on every admitted patient [143].

The effect of screening on ICU admission on acquisition and infection rates is mainly documented for VRE/MRSA [144–151]. Few studies focused on ESBL-GNB or *C. difficile* [152–155]: Due to the increasing prevalence of VRE in the Unites States, the Centers for Disease Control and Prevention (CDC) [156], 1995, and the Society for Healthcare Epidemiology of America (SHEA) [139], 2003, recommended VRE screening on hospital admission with subsequent isolation of colonised patients [52, 157–162]. A recent randomised trial did not find an additional benefit of universal screening for MRSA/VRE on ICU admission and strict contact precautions compared to pre-existing practice (standard hand hygiene and use of gloves for contact with patient's mucous membranes, wounds, and body fluids) [144]. The limitation of this trial was poor compliance with hand hygiene and wearing of gloves and gowns in intervention ICUs, as well as application of barrier precautions in only 35.0–50.7% of all ICU patient-days due to late reporting [163]. The findings of this study were confirmed by another recent cluster-randomised cross-over trial including 20 medical and surgical ICUs in the Unites States [145]. Universal care with gloves and gowns did not reduce the acquisition of MRSA or VRE compared to contact isolation of colonised patients (difference in acquisition density for MRSA or VRE –1.71 acquisitions per 1,000 person-days; 95% CI -6.15–2.73; p = 0.57) [145].

A European study on 13 ICUs analysed the effect of different vertical and horizontal infection control strategies on acquisition density of VRE, MRSA, and ESBL-GNB [146]. After a 6 month baseline surveillance period (phase 1) starting in May 2008, hand hygiene improvement programmes and chlorhexidine body washing were implemented at all ICUs (phase 2), followed by a cluster-randomised trial (phase 3, until April 2011) analysing the additional effect of admission colonisation screening for VRE, MRSA, and ESBL-GNB with subsequent contact isolation of carriers on acquisition incidence. Interventions in phase 2 significantly reduced MRSA acquisition, but had no impact on VRE and ESBL-GNB. Additional screening with subsequent contact isolation of carriers (phase 3) – whether performed by rapid testing (PCR) or conventional testing with chromogenic media – did not further reduce the acquisition incidence of antimicrobial-resistant bacteria (MRSA, VRE, and ESBL-GNB). However, it has to be taken into account that these results are only generalisable to settings with sustained high level of compliance to hand hygiene and chlorhexidine body washing. In a study from our centre we could demonstrate that with the use of strict contact precautions (i.e., hand hygiene, gloves, gowns, single room) for every VRE-colonised patient (no active surveillance), the incidence of VRE at our university hospital decreased to zero, after multiple cases in the mid 90's [21].

Altogether, these studies show that screening with contact isolation of carriers might not be equally effective for different bacteria. The failure to reduce VRE and ESBL-GNB compared to MRSA may be partly explained by differences in colonisation characteristics [146]. In contrast to MRSA, VRE and ESBL-GNB mainly colonise the intestinal tract, which is not affected by chlorhexidine body washing [146]. Furthermore, the colonisation of the environment probably plays a much more important role in nosocomial enterococcal transmission than previously thought [30]. In addition, around 5% of healthcare workers are colonised with MRSA [164] and may also spread the pathogen adding to the difficulties to identify key factors for transmission.

Selective digestive tract decontamination (mainly vertical strategy)

Over the last years, the effect of selective digestive tract decontamination regimens on colonisation and infection rates of ICU patients has been studied using different non-absorbable antibiotics reducing intestinal carriage of mainly gram-negative bacteria (e.g., ESBL-GNB) but also *S. aureus* and yeasts, sparing the anaerobic flora [165].

In a large cluster-randomised trial from the Netherlands, selective digestive tract decontamination and selective oropharyngeal decontamination both significantly reduced incidence of ICU-acquired bacteremia and overall mortality [166]. A review article of 65 randomised-controlled trials and 11 meta-analyses showed a reduction in lower airway infections of 72%, bloodstream infection of 37% and overall mortality of 29% with the use of selective digestive tract decontamination regimens [165].

Only a few studies analysed the effect of selective digestive tract decontamination on VRE [167, 168], *C. difficile* [169, 170], and ESBL-GNB [171–176] colonisation or infection rate in critical ill patients. A recent randomised placebo-controlled trial showed a reduced rectal ESBL-GNB colonisation rate during an oral decontamination regimen with

colistin sulfate and neomycin sulfate for 10 days, but no effect 3–5 weeks after treatment [171]. The temporary effect could be of interest for certain high-risk populations such as oncological or surgical patients during vulnerable treatment phases [171].

The use of selective digestive tract decontamination has raised the concern of selection pressure and increase in antimicrobial resistance [177]. In a recent meta-analysis, however, equal prevalence of colonisation and infection with MRSA (OR 1.46; 95% CI 0.90–2.37), VRE (OR 0.63; 95% CI 0.39–1.02), aminoglycoside- (OR 0.73; 95% CI 0.51–1.05) and polymyxin-resistant GNB (OR 0.58; 95% CI 0.46–0.72) was noted in ICU patients with or without selective digestive tract decontamination [177]. Ecological data from 38 Dutch ICUs showed reduction in resistance rates with the use of selective oropharyngeal and digestive tract decontamination for all antimicrobial agents included in the analysis (ciprofloxacin, ceftazidime, cefotaxime/ceftriaxone, tobramycin, colistin) [178]. The lack of documented resistance could be explained by reduced antibiotic treatment rates for hospital-acquired infections. An important limitation is the short follow-up of studies, possibly not allowing detection of long-term changes in resistance [166, 177–182].

Vaccination (vertical strategy)

Developing vaccines against nosocomial pathogens such as *S. aureus* and enterococci has been complicated, as the mechanisms leading to protective immunity are only partly understood [183]. A temporary effect has been shown for a *S. aureus* conjugate vaccine in dialysis patients [184]. Other vaccines are currently being investigated; the most recent *S. aureus* vaccine (V710) failed to prevent surgical site infections after cardiothoracic surgery [185]. To date, enterococcal vaccines have been solely evaluated in animal studies [186–188] and its clinical use needs to be determined. The importance of humoral immune response to *C. difficile* toxins A and B [189] lead to the development of vaccines as a promising strategy against *C. difficile* infection. Different vaccines, containing toxoid A and/or B, have been proven safe, immunogenic, and possibly effective in the prevention of *C. difficile* infection and recurrence [190–194].

Chlorhexidine body washing (horizontal strategy)

The effect of chlorhexidine body washing on bloodstream infection rates and on cross-transmission of multidrug-resistant bacteria has been demonstrated in a cluster-randomised trial in 9 ICUs in the United States showing a significant reduction in hospital-acquired bloodstream infections of 28% with daily chlorhexidine body washing [195]. Of note, the reduction was significant only for coagulase-negative staphylococci and not MRSA or VRE. In contrast, a recent meta-analysis showed significantly lowered MRSA/VRE colonisation and infection densities in patients treated with daily chlorhexidine body washing compared to patients without (incidence rate ratio 0.51; 95% CI 0.36–0.73 and 0.57; 95% CI 0.33–0.97; for VRE colonisation and VRE infection, respectively) [196]. So far, only a few studies have addressed the effect of chlorhexidine body washing on ESBL-GNB [146, 149] and *C. difficile* [197, 198] acquisition, not allowing the drawing of definite conclusions for these pathogens.

Antimicrobial stewardship

Antimicrobial stewardship programs encompass interventions promoting a responsible use of antimicrobial agents in order to improve patient outcome, enhance patient safety, reduce antimicrobial resistance and cut health-care costs [199]. A recently published Cochrane systematic review showed that hospital-wide antimicrobial stewardship is safe, reduces antimicrobial resistance and hospital-acquired infection incidence [200]. In a current meta-analysis, implementation of antimicrobial stewardship programmes on ICUs, reduced antibiotic use up to 55.4% and direct antibiotic costs by 4.6–72.3 US$ per patient-day [201]. More importantly, antimicrobial stewardship was associated with reductions in antimicrobial resistance and adverse events, without compromise of short-term clinical outcome [201].

The value of antibiotic cycling or mixing on prevention of multidrug-resistance is unknown [202]. A recent Spanish interventional study in ICU patients with ventilator-associated pneumonia indicated that mixing might prevent the emergence of antimicrobial resistance [203]. Nevertheless, currently, no definitive conclusions can be drawn on the value of antibiotic cycling/mixing [202–207].

Gaps in knowledge

The degree and full extent of health consequences following changes in the human microbiome have only recently been studied and are still little understood. Few studies could show a change in nosocomial infection rate after interventions targeting colonisation with VRE, ESBL-GNB and *C. difficile*. The rise of multidrug-resistant bacteria in the colonising flora of hospitalised patients but also healthy persons is one of the major challenges of future medicine. Internationally standardised, evidence-based and mandatory policies to control the emergence of multidrug-resistance are urgently needed and the ideal “bundle” of infection control strategies in ICU patients has yet to be defined.

Conclusion

The shift from a normal intestinal microbiome to a ‘selected’ gut flora dominated by antibiotic-resistant enterococci, ESBL-GNB and *C. difficile* in critically ill patients is a major risk factor for subsequent infection. The global rise of antimicrobial resistance, the increasing spread of bacteria and antimicrobial-resistance genes in the community and healthcare setting endanger patients at highest risk for nosocomial difficult-to-treat infections, especially in the ICU or on transplant units. Known infection control measures such as hand hygiene and antimicrobial stewardship urgently need to be implemented all over the world. New infection control measures need to be studied in order to halter further spread of resistant bacteria. The concurrent paucity of new antibiotics being developed stresses the importance of preventive measures even more. Especially horizontal infection control strategies could gain in im-

portance as new multidrug-resistant pathogens constantly emerge.

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Figures (large format)

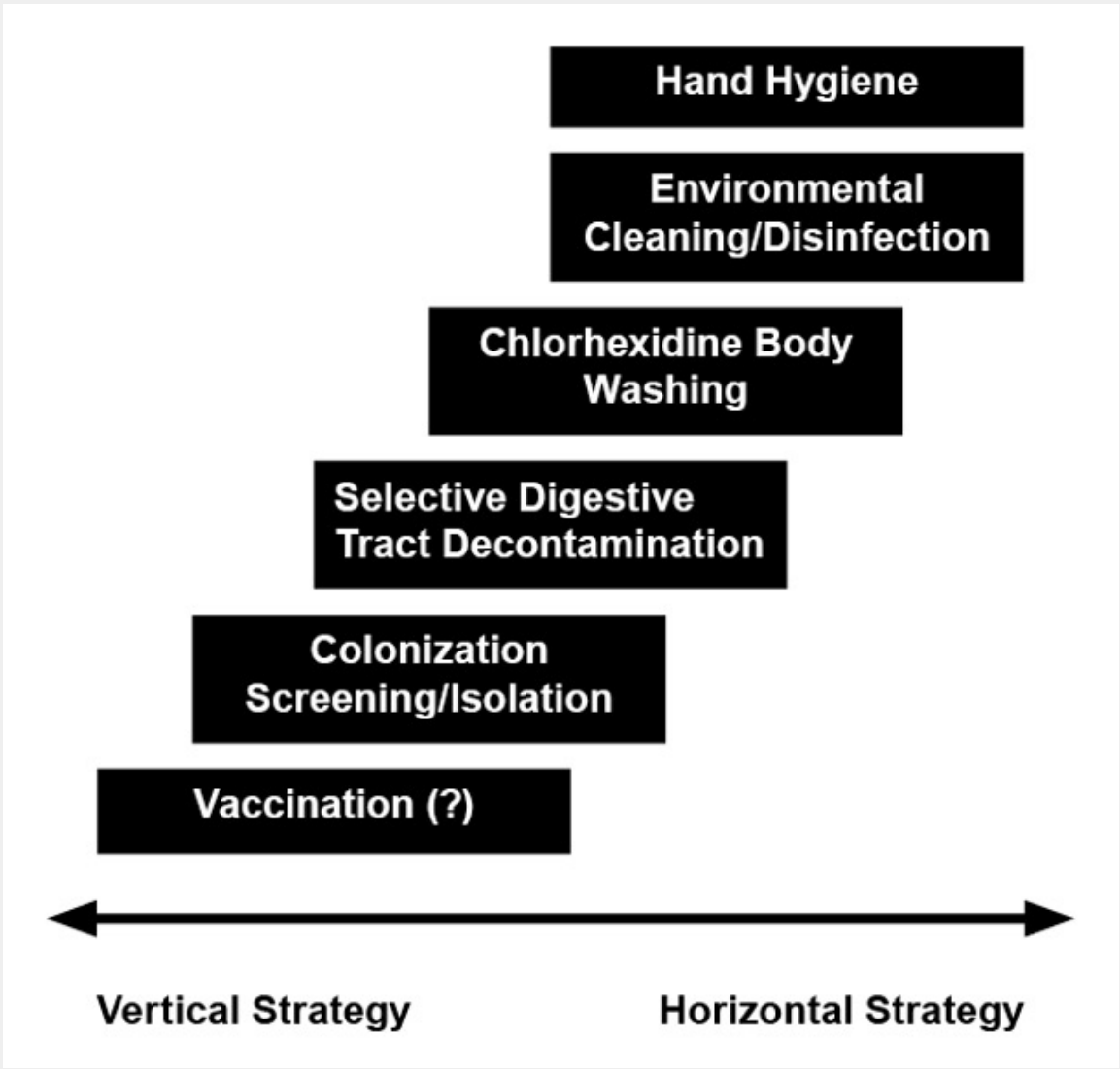

Figure 1

Infection control strategies in intensive care units: A continuum.
Infection control in intensive care units can involve vertical and horizontal strategies [134, 135]. While vertical interventions aim to reduce colonisation and infection with a certain pathogen, horizontal interventions try to minimise the spread of pathogens in general by using a universal approach [134, 135]. For prevention of bacterial infection in ICU patients, vaccines may be of interest in the future.