pREVention and management tools for rEducing antibiotic Resistance in high prevalence SEttings (REVERSE) - analysis plan for a stepped wedge type II effectiveness-implementation cluster randomized trial of Infection Prevention and Control and Antimicrobial Stewardship to prevent healthcare associated carbapenem resistant infections

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Abstract

Background Antimicrobial resistance (AMR) is a major threat to healthcare in Europe with carbapenem resistant organisms being categorized as a critical group by the World Health Organisation (WHO). The majority of carbapenem infections occur within healthcare settings. Infection prevention and control (IPC) and antimicrobial stewardship (AMS) have each been shown to reduce healthcare-associated infections (HAIs) and resistance but have largely been implemented and evaluated as separate programmes. The REVERSE (pREVention and management tools for rEducing antibiotic Resistance in high prevalence SEttings) project evaluates the sequential and cumulative implementation of bundled microbiology and diagnostic stewardship (MDS), IPC and AMS interventions in hospitals with a high prevalence of carbapenem-resistant Gram-negative bacteria.

Methods/ Design

REVERSE is a prospective, multicentre, stepped-wedge cluster-randomised trial (SW-CRT) with a type II hybrid effectiveness-implementation design, conducted in 24 hospitals (clusters) in Greece, Italy, Romania and Spain. Hospitals were recruited based on size, annual admissions and national prevalence of carbapenem-resistant healthcare-associated infections before the baseline phase. Healthcare workers on participating wards are the target population, and adult inpatients on these wards are the outcome population. All hospitals start in a baseline phase and progress through an MDS phase before sequentially implementing IPC and AMS interventions. Hospitals were randomised to one of four sequences (six hospitals each) over 16 quarterly periods, stratified by country and implementation condition (basic or enhanced implementation support). Owing to the nature of the interventions, neither hospitals nor study personnel are blinded. The primary outcome is the incidence density (per 1,000 patient-days) of HAIs caused by carbapenem-resistant Enterobacterales, Acinetobacter baumannii and Pseudomonas aeruginosa. The trial is powered to detect a 25% reduction in the primary outcome during the IPC phase and a further 10% reduction during the IPC and AMS phase. All 24 hospitals and 16 periods will be analysed according to the intention-to-treat principle, using generalised linear mixed models with a negative binomial distribution for count outcomes and mixed-effects logistic regression for binary outcomes. As all interventions are based on best practice and none is delivered directly to patients, no adverse events are anticipated; in-hospital mortality and readmission will be analysed as safety outcomes.

Discussion

REVERSE is among the largest randomised trials to examine the effect of combined IPC and AMS interventions, together with implementation support, on carbapenem-resistant HAIs in high-prevalence European settings. Its findings will inform how coordinated programmes with implementation support can reduce carbapenem-resistant infections.

Trial registration

ISRCTNISRCTN12956554. Prospectively registered on 11 November 2021.

Ethics approval

REVERSE was granted a positive evaluation by the Cantonal Ethics Commission in Zurich, Switzerland and was approved by the local ethics committees in the participating centers.

Introduction

Antimicrobial resistance (AMR) in bacteria is driven by selection pressure following exposure to antimicrobials. In healthcare settings, resistance can then spread further, either through transmission of resistant organisms between patients or through horizontal transfer of resistance genes between bacteria [1]. Infections caused by antimicrobial-resistant organisms pose a serious challenge to healthcare worldwide, resulting in increased morbidity, mortality and cost [2]. Carbapenem resistance is particularly concerning, as these bacteria are difficult to treat and continue to spread [3]. WWithin Europe, the burden is unevenly distributed with countries in southern, central, and eastern Europe reporting higher proportions of carbapenem resistance [3].

Healthcare organisations are complex adaptive systems, and AMR arises from pressures both within and beyond them [1,4]. Acute care hospitals nevertheless remain a critical focal point, because they combine three key drivers of resistance: high antimicrobial use, vulnerable patients, and frequent contact with multiple healthcare workers [5]. TThe burden of resistance is also concentrated in these settings as an estimated 63.5% of infections with antimicrobial-resistant bacteria are healthcare-associated [6]. Preventing the further emergence and spread of AMR within acute care facilities is therefore an urgent priority.

Infection prevention and control (IPC) and antimicrobial stewardship (AMS) programmes have each been shown to reduce healthcare-associated infections (HAI) and resistance. For IPC, the SENIC study established surveillance and control activities as the foundation of IPC programmes, finding that hospitals with effective programmes had approximately 30% fewer HAIs [7]. A hospital-wide hand hygiene (HH) campaign subsequently reduced HAI rates and methicillin-resistant Staphylococcus aureus (MRSA) transmission, establishing HH as a cornerstone of IPC [8]. Bundled interventions extended this toolkit further, with a multicomponent ICU programme substantially reducing catheter-related bloodstream infections [9]. Drawing on these and many other studies, the SIGHT systematic review defined ten key components of effective IPC, which informed the World Health Organization's eight core components of IPC programmes [10,11].

For AMS, studies linked higher antimicrobial consumption to higher resistance rates, providing the rationale for optimising antimicrobial use [12]. Stewardship interventions, including restrictive and persuasive strategies, have since been shown to improve prescribing and reduce resistance and Clostridioides difficile infection [13–15].

Despite their shared goals, IPC and AMS have largely been implemented and evaluated as separate programmes, even though evidence suggests they act synergistically. AMS programmes achieved greater reductions in antibiotic-resistant infections and C. difficile infections when combined with IPC measures than when delivered alone [15]. Arguments for both strategies to be pursued in parallel and integrated models such as the AID (antimicrobial, infection prevention and diagnostic) stewardship framework have been proposed [16,17]. This integration also appears feasible in resource-limited settings [18].

Both IPC and AMS depend on timely and reliable microbiological diagnostics. Diagnostic stewardship aims to improve the process of ordering, performing, and reporting diagnostic tests to facilitate diagnosis and treatment [19]. Accurate and harmonised antimicrobial susceptibility testing (AST) is required for both individual patient treatment and comparable resistance surveillance. Across Europe, wide adoption of EUCAST standards has improved this comparability [20]. However, laboratory capacity and capability still vary across European hospitals [21].W hile overall capacity has improved across countries, diagnostic test utilisation and AMR monitoring scores lag behind [20]. As these gaps can limit the potential of IPC and AMS programmes, strengthening and harmonising microbiological capacity is a prerequisite for integrated IPC and AMS.

Clinical cultures only identify patients with symptomatic infection. If no screening is done, resistant organisms may still spread undetected through asymptomatic carriers [22]. Point prevalence screening surveys (PPS), in which all inpatients on a given day are sampled for carriage of resistant organisms, can provide a glimpse into this hidden reservoir. This snapshot of colonization rates can provide a baseline before an intervention and a measure of its effect afterwards [23].

Further, the success of IPC and AMS activities is highly dependent on the quality of their implementation, requiring organisational and individual behaviour change from multiple professions while balancing multiple competing priorities. Whereas implementation has traditionally been studied subsequent to clinical effectiveness, novel hybrid effectiveness-implementation studies that evaluate clinical effectiveness and real-world implementation simultaneously are gaining attention, particularly for IPC and AMS [24].

The REVERSE (pREVention and management tools for rEducing antibiotic Resistance in high prevalence SEttings) project responds to these interdependent, systemic challenges. Microbiology and diagnostic stewardship (MDS), IPC and AMS are sequentially implemented in a SW-CRT in 24 hospitals in Greece, Italy, Romania and Spain with the aim of reducing carbapenem-resistant Gram-negative healthcare-associated infections. In parallel, two implementation support strategies are compared using a hybrid type II effectiveness-implementation design [25,26]. This article describes the statistical analysis plan (SAP) for the REVERSE trial; the protocol for the embedded implementation trial has been published separately [26].

Research Questions

REVERSE will address two research questions:

1. Effectiveness: Does the sequential and additive implementation of IPC and AMS programmes result in a significant reduction in healthcare-associated infections (HAIs) caused by carbapenem resistant bacteria, compared with the baseline and MDS phases?

2. Implementation: Does enhanced implementation support lead to a greater reduction in HAI caused by resistant bacteria than basic implementation support?

Methods

Study Design

REVERSE is a prospective, multicentre, SW-CRT with a hybrid type II effectiveness-implementation design, conducted in 24 hospitals in four European countries (Greece, Italy, Romania and Spain). All hospitals are in settings with a high prevalence of multidrug-resistant organisms (MDROs), particularly carbapenem-resistant Gram-negative bacteria. The trial was prospectively registered with ISRCTN on 11 November 2021 [27].

Justification for a SW-CRT

As the interventions target hospital workers rather than individual patients, a cluster-randomised design was necessary with a cluster being a hospital. A stepped-wedge design was chosen as a parallel design with 24 hospitals would have lacked sufficient power given higher intracluster correlation (ICC) and cluster autocorrelation (CAC) within hospitals for process variables such as guidelines [28]. Additionally, this would have required control hospitals to commit to five years of participation without receiving any intervention. The interventions were also labour-intensive for the project team, so staggered delivery was necessary. Lastly, a crossover design would have been inappropriate, as the interventions aimed to create lasting organisational change that could not be withdrawn.

Study Periods

All hospitals will start in the baseline phase at month 0 and progress through the interventions in the same sequence (Figure **1**). TThe first cohort will enter the Microbiology and Diagnostic Stewardship (MDS) phase after six months, with each subsequent cohort starting three months later. The IPC intervention will begin six months after the start of the MDS phase, and the AMS intervention 12 months after the start of IPC. The MDS phase will aim to assess laboratory capacity and harmonise testing (particularly for carbapenem resistance) rather than to change clinical practice. Therefore, it will be treated as part of the baseline in the analysis. All hospitals will ultimately receive all interventions, with control provided by the stepped-wedge design.

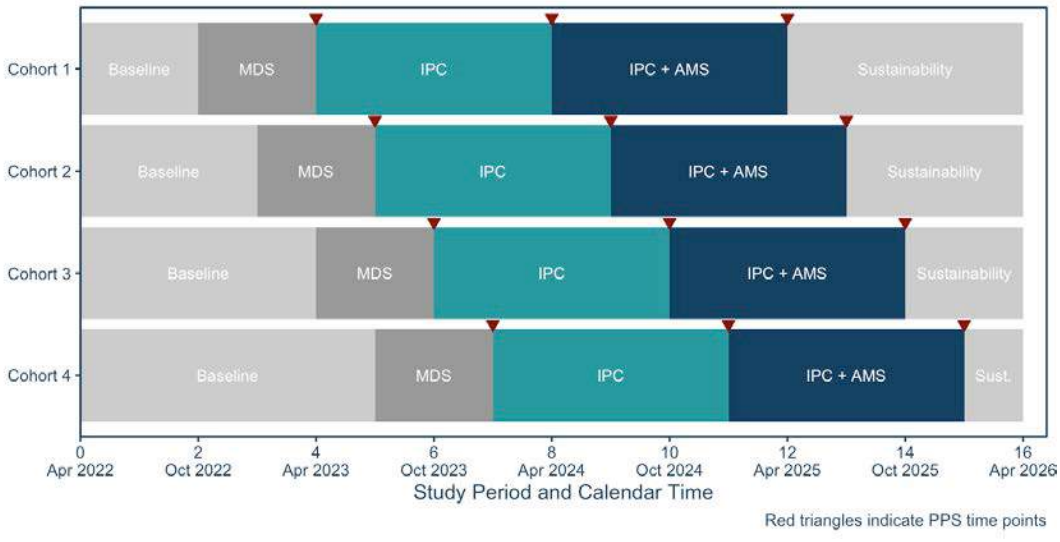


Figure 1: Stepped wedge design for the four cohorts in REVERSE

Study Population

The target population will be healthcare workers on participating wards ("REVERSE" wards) in participating hospitals. The outcome population will comprise all adult inpatients on REVERSE wards in participating hospitals.

Inclusion criteria for outcome population: Adult inpatients hospitalised in intensive care, internal medicine (including all subspecialty wards and infectious diseases), haematology-oncology, or surgery (including transplant units).

Exclusion criteria for outcome population: Patients on other wards, outpatients, and patients under 18 years of age.

Hospitals will be recruited based on the following criteria:

Hospital criteria:

- Acute care hospital with internal medicine, haematology-oncology, and surgery units
- Medium to large size (ideally more than 400 acute care beds involved in the project)
- Incidence density of HAI due to carbapenem-resistant Enterobacterales (CRE), carbapenem-resistant Pseudomonas aeruginosa (CRPA) and carbapenem-resistant Acinetobacter baumannii (CRAB) combined must be >0.5 per 1000 patient-days
    - 75 healthcare associated infections per year due to Gram-negative multidrug-resistant organisms (MDRO) (based on 25'000 admissions per year and an average length of stay of 6 days)
- At least 20,000 admissions in acute care per year in REVERSE wards

Administration criteria:

- Hospital management must pledge to support the interventions
- Hospital management must provide data on costs of laboratory testing, IPC interventions, and antimicrobials
- Hospital management agrees that employees are interviewed upon informed consent for qualitative research

Microbiology criteria:

- Sufficient capacity of AMR testing by state-of-the-art methodologies
- An automated system for blood culture testing

Programme criteria:

- Established IPC team (at least one nurse and physician with dedicated time)

Other criteria:

- Experience within previous European or national patient safety projects (AMR, IPC)
- Not too many ongoing, parallel clinical trials

Justification of study population: REVERSE will focus on acute care hospitals because they are a major source of MDROs. The burden of antimicrobial resistance is higher in hospitals than in the community and, within hospitals, higher in healthcare-associated than in community-acquired infections [6]. The four participating countries will be selected for their high prevalence of CRE, CRAB and CRPA in the 2016/17 ECDC point prevalence survey [29].

Clinical Interventions

The clinical interventions, or IPC and AMS programmes, will be implemented as bundles combined with professional implementation support. Both will be multifaceted and tiered, comprising best-practice procedures and technology-based interventions, and will primarily target healthcare professionals and other hospital staff. The interventions and associated standard operating procedures (SOPs) are described in **Supplementary section 1**.

IIn addition to the clinical interventions, point prevalence surveys (PPS) for carbapenem-resistant bacterial colonisation will be conducted at three time points in the study (before IPC (i.e. baseline), before AMS, and before sustainability) (see Figure **1**). All patients admitted to the REVERSE ward will be eligible, with an expected 250 swabs per hospital per PPS. All swabs will be analysed at a central laboratory. Details for swab collection and analysis can be found in **Supplementary section 2** and in Verhagen et al (submitted manuscript)[30].

Implementation Condition

All participating hospitals will be randomised to one of two implementation conditions, basic and enhanced. Both conditions will assess tailoring as an implementation strategy [26], where hospitals in the basic condition will independently tailor their IPC and AMS implementation, while those in the enhanced condition will receive time-limited external facilitation to guide their tailoring practice.

Randomisation

Randomisation will be performed at hospital level, stratified by country for both baseline duration and implementation condition (sequential randomisation). The randomisation for implementation condition will be constrained such that each of the four cohorts contains three hospitals in each implementation condition (Figure **2**). Across all cohorts, three hospitals per country will be assigned to each implementation condition, giving 12 hospitals in the enhanced and 12 in the basic implementation condition. All hospitals will receive at least basic implementation support.

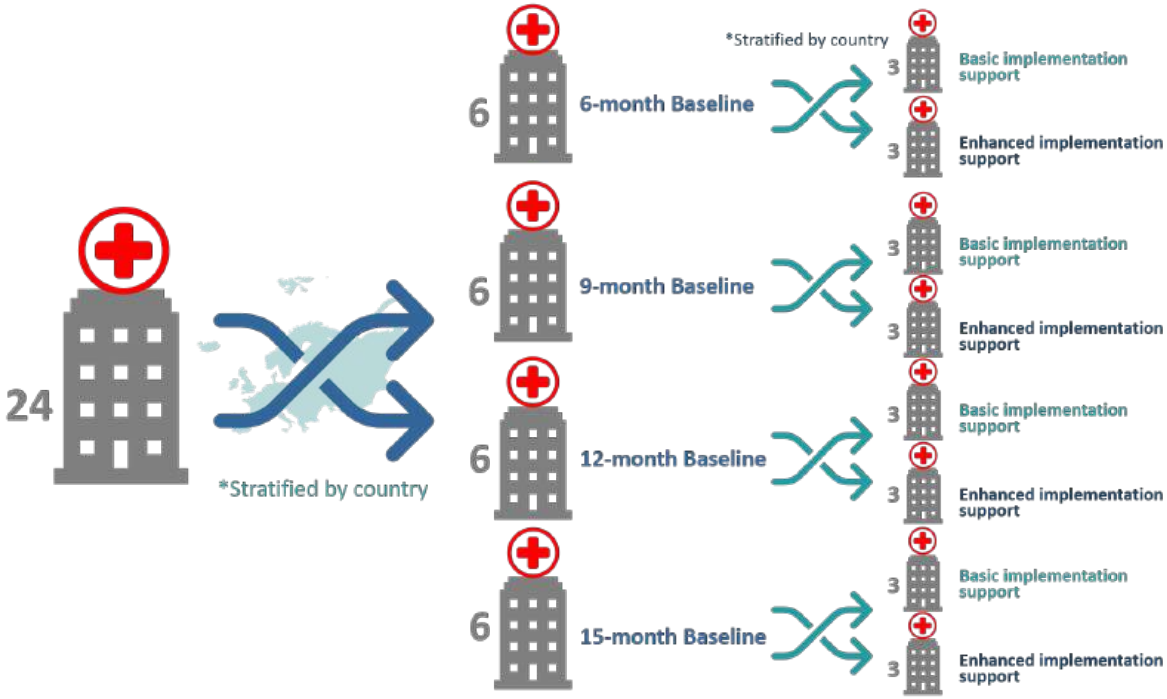


Figure 2: Randomisation procedure and stratification variables used in REVERSE

Blinding

Owing to the nature of the interventions and the sharing of the study protocol, participating sites will not be blinded to their cohort or implementation condition. Sites will not be explicitly told their implementation condition; however, the study protocol states that only sites in the enhanced condition will receive site visits. Therefore, it is likely the REVERSE staff in the hospitals will be aware of their implementation assignment.

Data entry will be done by hospital study staff, who will also be involved in implementing the interventions. These personnel will also not be blinded to the study phase. Data analysts will also not be blinded.

Data collection

HAI data

Microbiologically confirmed HAIs caused by CRE, CRAB, CRPA, extended-spectrum β-lactamase (ESBL)-producing Enterobacterales, methicillin-resistant Staphylococcus aureus (MRSA) or vancomycin-resistant enterococci (VRE) werewill be documented prospectively in a REDCap database hosted by the University Hospital Zurich (USZ) [31,32]. Eighteen of the 24 hospitals will enter data directly into the USZ database. Due to more stringent data-sharing legislation in Italy, a separate REDCap database will be set up in each Italian hospital. Clinical, microbiological and antimicrobial data will be collected concurrently along with HAI source (current stay, current hospital, or other hospital). The full list of variables is provided in **Supplementary section 3**.

HAIs will be defined according to the ECDC point prevalence survey protocol version 5.3 throughout the study. The definition will remain consistent across study periods.

Positive cultures with the same organism within 14 days of an initial episode will not be recorded as new episodes (e.g., a patient with MRSA bacteraemia for five days would be recorded as a single

bloodstream infection). Where a culture yields multiple relevant bacteria, up to three will be recorded.

HAI data will be collected from April 2022 to March 2026.

Hospital Administrative Data

Administrative data (e.g., number of beds, patient-days, admissions, in-hospital mortality) will be collected quarterly, for both the entire hospital and, where available, for REVERSE wards, using a pre-labelled Excel template. The full list of variables is provided in **Supplementary section 4**. All hospitals will be able to provide patient-days at a ward level.

Antimicrobial Use Data

Antimicrobial use data will be extracted quarterly from hospital pharmacy systems using a pre-labelled Excel template, for the entire hospital and, where available, for REVERSE wards. The full list of antimicrobials is provided in **Supplementary section 5**. The antimicrobials will be chosen based on commonly used antimicrobials for surgical prophylaxis, treatment of healthcare associated infections, and treatment of the six multidrug resistant organisms of interest for REVERSE (CRAB, CRE, CRPA, ESBL-E, MRSA, and VRE).

Data Quality and Completeness

Data completeness will be checked quarterly with regular feedback to each centre. Delays, errors and outliers will be discussed with REVERSE study staff.

Where a variable could not be obtained for REVERSE wards specifically despite all efforts, hospital data will be used, scaled in proportion to the number of beds included in REVERSE. This will not apply to HAI data, which will be collected prospectively at ward level. Secondary outcomes such as healthcare associated *Clostridioides difficile infection*, alcohol-based handrub (ABHR) consumption, mortality and antimicrobial consumption will be analysed at hospital level and, where available, at the REVERSE ward level.

Data Confidentiality and Protection

All patient-level data will be entered only within REDCap (see Data collection and follow-up). The hospitals in Greece, Romania, and Spain will enter their data directly into the database hosted by the University Hospital Zürich (USZ). Due to more stringent data sharing regulations in Italy, each hospital in Italy will host its own REDCap database with a shared data dictionary and codebook. Data will be pseudonymised and transferred to Zürich at the end of the study. Hospital, ward and antimicrobial use data will be extracted from administrative and pharmacy systems and submitted separately. All data in Zürich, including the REVERSE analysis repository, will be stored on USZ or University of Zurich servers. REVERSE data will be confidential and shared only within the consortium.

Outcomes

Analysis Population

The primary analysis will include attributable HAIs only, defined as the subset of HAIs ascribed to the reporting hospital [2]. The denominator will be patient-days on REVERSE wards.

Primary Outcome

Incidence density (per 1,000 patient-days) of HAIs due to CRE, CRAB and CRPA, combined as a composite outcome.

Secondary Outcomes

1. Quarterly proportion of attributable HAIs due to CRE, CRAB and CRPA
2. Incidence density (per 1,000 patient-days) of attributable HAIs due to CRE, CRAB, CRPA, ESBL-E, MRSA, and VRE individually
3. Incidence density (per 1,000 patient-days) of healthcare-associated bloodstream infections caused by MDROs
4. Incidence density (per 1,000 patient-days) and quarterly proportion of attributable HAIs due ESBL-E, MRSA and VRE
5. Incidence density (per 10,000 patient-days) of healthcare associated *Clostridioides difficile* infection
6. Blood culture sets performed per 1,000 patient-days
7. Prevalence of CRE, CRAB, and CRPA colonisation at the end of baseline, at the end of the infection prevention and control programme, and at the end of the antibiotic stewardship programme
8. Stool tests for *C. difficile* performed per 1,000 patient-days
9. ABHR use (litres) per 1,000 patient-days
10. Antimicrobial use in defined daily doses (DDD) per 100 patient-days a. DDD per 100 patient-days by intravenous and oral route (possible effect of the AMS intervention in switching from IV to oral) b. DDD per 100 patient-days by WHO AWaRe category [33] (possible effect of increasing Access medications and decreasing RESERVE medications) c. ATCJ01 DDDs per 100 patient-days to judge the effect of the AMS programme on overall antimicrobial use
11. In-hospital all-cause mortality
12. Hospital readmissions per quarter
13. Mean Length of hospital stay
14. Cost effectiveness of both the interventions and their implementation
15. Implementation outcomes (feasibility, acceptability, sustainability) will be measured and analysed as described in Albers et al. [26].

Statistical Methods

Data Preparation

REDCap data and hospital Excel files will be imported directly into R. HAI data from the Italian hospitals will be pseudonymised locally and submitted as Excel files for merging (see **Supplementary section 6** for the pseudonymisation procedure).

General Principles

All analyses will follow the intention-to-treat principle. All 24 hospitals will be analysed according to their allocated sequence and implementation condition, regardless of which interventions are implemented or of any delay in implementation. Both stratification variables (country and implementation condition) will be included as fixed effects in all models. All tests will be two-sided at α = 0.05, and estimates will be reported with 95% confidence intervals unless otherwise stated. No interim analysis is planned. All analyses will be performed in R [34].

Analysis of Count Outcomes

All HAI outcomes will be analysed as count data. These are the primary outcome, other MDRO infections, *Clostridioides difficile* infections and MDRO bloodstream infections (BSIs). Alcohol-based handrub consumption, antimicrobial consumption, and numbers of blood cultures and stool tests will likewise be analysed as counts.

Incidence rates will be shown graphically for all 24 hospitals combined, by country and by implementation condition. Rates will be expressed per 1,000 patient-days for MDROs, per 10,000 patient-days for *C. difficile*, and as defined daily doses (DDD) per 100 patient-days for antimicrobial use.

The primary analysis will use a generalised linear mixed model with a negative binomial distribution, fitted to counts aggregated by cluster-period [35,36]. Fixed effects will include the intervention indicators, implementation condition, country, and calendar time, modelled as a linear term in quarters. Random effects will include a random intercept and slope for each cluster [37,38]. The logarithm of patient-days will be used as the offset. Each intervention will be coded as a time-dependent, cluster-specific binary indicator: 0 during the baseline and MDS phases, and 1 from the start of that intervention phase onwards. will be grouped into the baseline phase as it will target laboratory capacity and serve to improve detection of MDRO bacteria. The MDS intervention could hypothetically increase the incidence rate (by increasing testing and detection), but would not have an effect on MDRO transmission.Implementation condition will be coded as a factor with basic support as the reference starting at the same time as the IPC intervention. This will replicate the study conditions accurately as implementation support will only start with the interventions. Seasonal variation will be modelled using sine and cosine terms for an annual cycle, $sin(2\pi t/4)$ and $cos(2\pi t/4)$, where t is calendar time in quarters. Intervention effects will be reported as adjusted RRs with 95% confidence intervals.

In-hospital mortality and readmission rates

In-hospital mortality and readmission will be shown graphically as proportions over time for all 24 hospitals combined, by country and by implementation condition. Adjusted analyses will use mixed-effects logistic (binomial) models with the same fixed and random effects as the count outcome models, and results will be reported as odds ratios.

As mortality and readmission are available only on the hospital level, an additional analysis adjusting for the proportion of beds in REVERSE will be done.

Proportion of patients colonised with carbapenem-resistant bacteria

A screening swab growing any carbapenem-resistant organism (CRE, CRAB or CRPA) will be classified as positive. Swabs growing more than one resistant species will be counted once. Descriptive analyses will report the proportion of positive swabs for each point prevalence survey (PPS) for all 24 hospitals combined, by country and by implementation condition, both overall and by species.

PPS results will be analysed using mixed-effects logistic regression. Country, calendar time, phase (before IPC, after IPC, after IPC plus AMS), length of stay and ward will be fixed effects. Random intercepts will be included for each cluster and for each cluster-survey wave. Marginal predicted probabilities will also be reported.

Missing Data

Missing clinical data will not be imputed; analyses will be based on available data.

Other Analyses

Incidence densities and proportions will be calculated and reported separately for each resistant organism. Separate models will also be fitted for each organism (CRE, CRAB, CRPA, ESBL-producing Enterobacterales, MRSA and VRE) to explore whether intervention effects differ between them. As sensitivity analyses, we will fit a model that includes MDS as a separate intervention, and a model that uses all HAIs instead of attributable HAIs.

Exploratory analyses will account for the extent of implementation. IPC implementation will be quantified using an IPC score (**Supplementary section 7**), aand AMS implementation by the number of audit interventions and the percentage of recommendations accepted. To allow for a transition period, an additional model will code the first period after the start of each intervention as 0.5, representing an implementation phase.

The primary model will also be extended to include an interaction term between the implementation condition and interventions, country and interventions, and wards and interventions. Stratum-specific rate ratios for enhanced support will be reported.

Sample size

Based on data and modelling from the 2016/17 ECDC point prevalence survey, the estimated mean incidence densities of HAIs due to the CRE/CRAB/CRPA composite were 2.99, 0.73, 0.62 and 0.51 per 1,000 patient-days in Greece, Italy, Romania and Spain, respectively. Assuming the lowest incidence density (0.5 per 1,000 patient-days), a cluster autocorrelation coefficient (CAC) of 0.9, four sequences, an average of 25,000 admissions per hospital per year, power of 80% and an two sided alpha of 0.05, the number of hospitals required for each hypothesised effect was:

1. 25% reduction in HAIs with IPC alone: 2.3 hospitals
2. Additional 10% reduction with AMS added to IPC: 19.9 hospitals
3. Additional 15% reduction with enhanced implementation support: 9.8 hospitals

Twenty-four hospitals together will provide sufficient power for all three primary comparisons: (1) IPC versus baseline; (2) IPC plus AMS versus baseline; and (3) enhanced versus basic implementation support.

Ethical issues

The Cantonal Ethics Committee of Zurich, Switzerland, determined that a formal ethics evaluation was not required (AO_2021-00078) and issued a positive statement to facilitate approval at the other centres. All 24 hospitals received ethics approval. The requirement for individual informed consent was waived by the ethics committees of all 24 participating hospitals for the surveillance data. In Italy informed consent was required for the point prevalence surveys.

Discussion

This statistical analysis plan (SAP) describes the planned analyses of the REVERSE trial, a hybrid type II effectiveness-implementation study using a stepped wedge cluster-randomised trial evaluating the sequential implementation of IPC and AMS bundles, with basic or enhanced implementation support, in 24 acute care hospitals in four European countries with a high prevalence of carbapenem-resistant Gram-negative bacteria. It was prepared in line with published guidance on the content of SAPs and finalised before any comparative analyses of the primary outcome were undertaken [39].

Rationale

The primary outcome is a composite of HAIs caused by CRE, CRAB and CRPA. These bacteria are prioritised by the WHO and ECDC and share transmission pathways. A composite outcome increases statistical power and allows for analysis of all three as a primary outcome. Specific incidence densities and proportions for each bacteria will be reported as secondary outcomes to allow readers to assess whether effects are driven by a single organism.

The primary analysis is restricted to HAIs attributable to the reporting hospital. Infections acquired in other healthcare facilities cannot plausibly be influenced by interventions in the study hospital, and their inclusion would dilute any intervention effect. Similarly, the MDS phase is treated as part of the baseline period because its purpose was to assess laboratory capacity and harmonise microbiological testing rather than to change clinical practice. Since improved diagnostics could nevertheless increase the detection of resistant bacteria, a separate rate ratio for the MDS phase will be estimated as a sensitivity analysis.

In stepped-wedge designs the estimated effect is vulnerable to confounding by secular trends [35,40]. This is particularly relevant for REVERSE, as data collection began in 2022 during the COVID-19 pandemic. Additionally, AMR epidemiology continued to evolve, especially as the pandemic ended and travel recommenced. The primary model therefore adjusts for calendar time and seasonality, in addition to country and hospital-level effects. A negative binomial distribution was chosen to account for the over-dispersion expected in HAI counts across hospitals in different countries and quarters.

As a type II hybrid effectiveness-implementation study, REVERSE aims to assess both the clinical effectiveness of the interventions and the effect of the implementation strategy [25]. The comparison of enhanced with basic implementation support evaluates the effectiveness of the chosen implementation support strategies, and the supportive analyses incorporating IPC implementation scores and AMS audit data will help to establish whether the effect observed is related to the degree to which interventions were actually implemented. Modelling a transition period, in which the first one or two quarters after each intervention start are treated as partial exposure, reflects the expectation

that complex organisational interventions take time to become embedded in practice. By employing a hybrid effectiveness-implementation approach, the REVERSE study aims to accelerate and improve the translation of clinical IPC and AMS interventions into real-world practice in healthcare settings.

Strengths and limitations

REVERSE has several strengths. It is, to our knowledge, among the largest randomised evaluations of IPC and AMS interventions in European hospitals with a high prevalence of carbapenem resistance. HAIs were identified prospectively using standardised ECDC definitions that were kept constant throughout the study, and randomisation was stratified by country and implementation condition to ensure balance across cohorts. The stepped-wedge design ensured that all participating hospitals received all interventions, which supported recruitment and retention of hospitals over the four-year study period. The embedded implementation trial will generate further insights about effective approaches to tailoring implementation activities.

Several limitations should be considered when interpreting the results. First, owing to the nature of the interventions, neither hospitals nor study staff could be blinded to the study phase. Although the primary outcome requires microbiological confirmation, which reduces the risk of biased ascertainment, surveillance intensity and diagnostic practices may change as a consequence of the interventions themselves. Blood culture and *C. difficile* testing rates are therefore included as secondary outcomes to help assess changes in diagnostic intensity. Second, hospitals and countries could have introduced other measures or projects that could support or compete with the resources needed for REVERSE. Third, hospital administrative and antimicrobial use data were collected in aggregate form, precluding adjustment for patient-level case mix in the analysis of mortality, readmissions and length of stay. Fourth, the use of separate REDCap databases in the Italian hospitals, necessitated by national data protection legislation, introduces an additional data-merging step with potential for inconsistencies, which was mitigated by harmonised data dictionaries. Finally, because the HAI definition was deliberately retained from ECDC protocol version 5.3, results may not be directly comparable with national surveillance data collected under later protocol versions.

Implications

If effective, the REVERSE bundles will provide evidence that coordinated IPC and AMS programmes can reduce carbapenem-resistant infections in hospitals where the burden of AMR is highest. The comparison of implementation conditions will also inform which implementation support conditions are effective. Results will be disseminated through peer-reviewed publications, conference presentations and feedback to participating hospitals and national stakeholders.

Trial Status

The trial was prospectively registered with ISRCTN on 11 November 2021 (ISRCTN12956554) [27] with data collection beginning in April 2022. This SAP (version 2, dated 18 September 2026) was finalised before database closure and analysis.

Funding

REVERSE has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 965265. The content of this document reflects only the authors' view. The European Commission is not responsible for any use that may be made of the information it contains.

References

[1] Holmes AH, Moore LSP, Sundsfjord A, Steinbakk M, Regmi S, Karkey A, et al. Understanding the mechanisms and drivers of antimicrobial resistance. The Lancet 2016;387:176–87. https://doi.org/10.1016/s0140-6736(15)00473-0.

[2] European Centre for Disease Prevention and Control. Assessing the health burden of infections with antibiotic-resistant bacteria in the EU/EEA, 2016–2020. Stockholm: ECDC; 2022.

[3] European Centre for Disease Prevention and Control. Antimicrobial resistance in the EU/EEA (EARS-net) - annual epidemiological report 2024. Stockholm: ECDC; 2025.

[4] Plsek PE, Greenhalgh T. The challenge of complexity in health care. BMJ 2001;323:625–8. https://doi.org/10.1136/bmj.323.7313.625.

[5] Struelens MJ. The epidemiology of antimicrobial resistance in hospital acquired infections: Problems and possible solutions. BMJ 1998;317:652–4. https://doi.org/10.1136/bmj.317.7159.652.

[6] Cassini A, Högberg LD, Plachouras D, Quattrocchi A, Hoxha A, Simonsen GS, et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the european economic area in 2015: A population-level modelling analysis. The Lancet Infectious Diseases 2019;19:56–66. https://doi.org/10.1016/s1473-3099(18)30605-4.

[7] HALEY RW, CULVER DH, WHITE JW, MORGAN WM, EMORI TG, MUNN VP, et al. THE EFFICACY OF INFECTION SURVEILLANCE AND CONTROL PROGRAMS IN PREVENTING NOSOCOMIAL INFECTIONS IN US HOSPITALS. American Journal of Epidemiology 1985;121:182–205. https://doi.org/10.1093/oxfordjournals.aje.a113990.

[8] Pittet D, Hugonnet S, Harbarth S, Mourouga P, Sauvan V, Touveneau S, et al. Effectiveness of a hospital-wide programme to improve compliance with hand hygiene. The Lancet 2000;356:1307–12. https://doi.org/10.1016/s0140-6736(00)02814-2.

[9] Pronovost P, Needham D, Berenholtz S, Sinopoli D, Chu H, Cosgrove S, et al. An intervention to decrease catheter-related bloodstream infections in the ICU. New England Journal of Medicine 2006;355:2725–32. https://doi.org/10.1056/nejmoa061115.

[10] Zingg W, Holmes A, Dettenkofer M, Goetting T, Secci F, Clack L, et al. Hospital organisation, management, and structure for prevention of health-care-associated infection: A systematic review and expert consensus. The Lancet Infectious Diseases 2015;15:212–24. https://doi.org/10.1016/s1473-3099(14)70854-0.

[11] World Health Organization. Guidelines on core components of infection prevention and control programmes at the national and acute health care facility level. Geneva: World Health Organization; 2016.

[12] Goossens H, Ferech M, Vander Stichele R, Elseviers M. Outpatient antibiotic use in Europe and association with resistance: A cross-national database study. The Lancet 2005;365:579–87. https://doi.org/10.1016/S0140-6736(05)17907-0.

[13] Schuts EC, Hulscher MEJL, Mouton JW, Verduin CM, Stuart JWTC, Overdiek HWPM, et al. Current evidence on hospital antimicrobial stewardship objectives: A systematic review and meta-analysis. The Lancet Infectious Diseases 2016;16:847–56. https://doi.org/10.1016/s1473-3099(16)00065-7.

[14] Davey P, Marwick CA, Scott CL, Charani E, McNeil K, Brown E, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database of Systematic Reviews 2017;2017. https://doi.org/10.1002/14651858.cd003543.pub4.

[15] Baur D, Gladstone BP, Burkert F, Carrara E, Foschi F, Döbele S, et al. Effect of antibiotic stewardship on the incidence of infection and colonisation with antibiotic-resistant bacteria and clostridium difficile infection: A systematic review and meta-analysis. The Lancet Infectious Diseases 2017;17:990–1001. https://doi.org/10.1016/s1473-3099(17)30325-0.

[16] Pulcini C, Collignon P. Hospital antimicrobial stewardship: The way forward. The Lancet Infectious Diseases 2017;17:1120. https://doi.org/10.1016/s1473-3099(17)30570-4.

[17] Dik J-WH, Poelman R, Friedrich AW, Panday PN, Lo-Ten-Foe JR, Assen S van, et al. An integrated stewardship model: Antimicrobial, infection prevention and diagnostic (AID). Future Microbiology 2015;11:93–102. https://doi.org/10.2217/fmb.15.99.

[18] Fofanah BD, Kamara IF, Kamara RZ, Musoke R, Tengbe SM, Kabego L, et al. Fighting antimicrobial resistance in a resource-limited setting: An integrated approach to infection prevention and antimicrobial stewardship is the “best buy.” Journal of Hospital Infection 2025;161:132–4. https://doi.org/10.1016/j.jhin.2025.02.023.

[19] Morgan DJ, Malani P, Diekema DJ. Diagnostic stewardship—leveraging the laboratory to improve antimicrobial use. JAMA 2017;318:607. https://doi.org/10.1001/jama.2017.8531.

[20] European Centre for Disease Prevention and Control. EU laboratory capability monitoring system (EULabCap): Report on 2021 survey of EU/EEA country capabilities and capacities. Stockholm: ECDC; 2023.

[21] European Centre for Disease Prevention and Control. EU laboratory capability monitoring system (EULabCap): Report on 2021 survey of EU/EEA country capabilities and capacities. Stockholm: ECDC; 2023.

[22] Smith DL, Dushoff J, Perencevich EN, Harris AD, Levin SA. Persistent colonization and the spread of antibiotic resistance in nosocomial pathogens: Resistance is a regional problem. Proceedings of the National Academy of Sciences 2004;101:3709–14. https://doi.org/10.1073/pnas.0400456101.

[23] Bauer A, Sturm H, Martus P, Brüggenjürgen B, Eberhardt H, Mayer E, et al. Can screening and decontamination procedures performed on an outpatient basis reduce colonization with staphylococcus aureus and mitigate associated complications in patients undergoing elective hospital procedures? A controlled intervention study (STAUfrei). Journal of Hospital Infection 2025;157:19–28. https://doi.org/10.1016/j.jhin.2024.12.001.

[24] Clack L, Schultes M-T, Albers B, Wolfensberger A. Hybrid effectiveness-implementation studies in infection prevention and infectious diseases: A narrative review. Clinical Microbiology and Infection 2026;32:1225–37. https://doi.org/10.1016/j.cmi.2025.10.022.

[25] Curran GM, Bauer M, Mittman B, Pyne JM, Stetler C. Effectiveness-implementation hybrid designs: Combining elements of clinical effectiveness and implementation research to enhance public health impact. Medical Care 2012;50:217–26. https://doi.org/10.1097/mlr.0b013e3182408812.

[26] Albers B, Caci L, Blum K, Boland G, Carrara E, Gentil PR, et al. Examining tailoring as an implementation strategy for reducing healthcare-associated infections across european acute care hospitals (REVERSE): Study protocol for a hybrid type 2 effectiveness-implementation trial. Trials 2025;26. https://doi.org/10.1186/s13063-025-09132-x.

[27] Sonpar A. Developing the tools to fight drug-resistant bacteria. Http://Isrctncom/ 2021. https://doi.org/10.1186/isrctn12956554.

[28] Campbell MK, Fayers PM, Grimshaw JM. Determinants of the intracluster correlation coefficient in cluster randomized trials: The case of implementation research. Clinical Trials 2005;2:99–107. https://doi.org/10.1191/1740774505cn071oa.

[29] European Centre for Disease Prevention and Control. Point prevalence survey of healthcare-associated infections and antimicrobial use in European acute care hospitals, 2016–2017. Stockholm: ECDC; 2023.

[30] Verhagen, E. R. and Boland, G. J. and van Mourik, M. S. M. and de Vries, D. D. and Fluit, A. C. and Carrara, E. and Hristea, A. and Rodríguez-Baño, J. and Daikos, G. L. and Sonpar, A. and Zingg, W. and Kluytmans, J. A. J. W. and REVERSE-study group author =. Carbapenemase-producing bacteria in european hospitals: A multinational point prevalence survey as part of the REVERSE trial 2026.

[31] Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. Journal of Biomedical Informatics 2009;42:377–81. https://doi.org/10.1016/j.jbi.2008.08.010.

[32] Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: Building an international community of software platform partners. Journal of Biomedical Informatics 2019;95:103208. https://doi.org/10.1016/j.jbi.2019.103208.

[33] World Health Organization. Web Annex C. WHO AWaRe (access, watch, reserve) classification of antibiotics for evaluation and monitoring of use, 2023. Geneva: World Health Organization; 2023.

[34] R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2025.

[35] Hussey MA, Hughes JP. Design and analysis of stepped wedge cluster randomized trials. Contemporary Clinical Trials 2007;28:182–91. https://doi.org/10.1016/j.cct.2006.05.007.

[36] Li F, Hughes JP, Hemming K, Taljaard M, Melnick ER, Heagerty PJ. Mixed-effects models for the design and analysis of stepped wedge cluster randomized trials: An overview. Statistical Methods in Medical Research 2020;30:612–39. https://doi.org/10.1177/0962280220932962.

[37] Girling AJ, Hemming K. Statistical efficiency and optimal design for stepped cluster studies under linear mixed effects models. Statistics in Medicine 2016;35:2149–66. https://doi.org/10.1002/sim.6850.

[38] Hooper R, Teerenstra S, Hoop E de, Eldridge S. Sample size calculation for stepped wedge and other longitudinal cluster randomised trials: Sample size calculation for stepped wedge trials. Statistics in Medicine 2016;35:4718–28. https://doi.org/10.1002/sim.7028.

[39] Gamble C, Krishan A, Stocken D, Lewis S, Juszczak E, Doré C, et al. Guidelines for the content of statistical analysis plans in clinical trials. JAMA 2017;318:2337. https://doi.org/10.1001/jama.2017.18556.

[40] Hemming K, Haines TP, Chilton PJ, Girling AJ, Lilford RJ. The stepped wedge cluster randomised trial: Rationale, design, analysis, and reporting. BMJ 2015;350:h391–1. https://doi.org/10.1136/bmj.h391.

Supplementary Material

Supplementary Section 1

Standard operating procedures

Hand hygiene

"Cleaning hands at the right times and in the right way" (WHO)

Title	Contact precautions
Document status	Approved by on
Version Number	V1
Authors	Aude Nguyen, Stephan Harbarth

Introduction

Hand hygiene (HH) is the cornerstone of standard precautions and the pillar of infection prevention. It is considered as the most effective way of preventing healthcare associated infections (HAI) through direct reduction in cross-transmission of pathogenic microorganisms, a cost-effective action, easy to perform, implemented in every hospital [1-5].

Even if it is difficult to quantify the isolated impact, as hand hygiene improvement is often part of a multifaceted bundle, the role of hand hygiene in the management/reduction of transmission of patients colonised or infected by multidrug resistant organisms (MDROs) is clearly recommended [6-8] and broadly agreed by all the international as well as society guidelines [9-11]. A systematic literature review done by WHO[12], identifying 39 papers, mostly focusing on the prevention and control of MRSA, more rarely CRE, concludes that the "*great majority of papers offer convincing evidence that improved hand hygiene practices lead to a reduction of HAIs and/or transmission or colonization by MDRO.*

Multiple barriers to achieve and maintain high hand hygiene compliance have been described such as environmental factors (for example access to alcohol hand rub), individual/personal factors as well as organizational/institutional factors (for example, workflow allowing proper hand hygiene).

Fig 8:

Table 1. Factors compromising hand hygiene compliance

Personal	Institutional	Resource-associated
Forgetfulness	Patient overcrowding	Limited availability of hand hygiene supplies
Habit	Work overload	Poor quality of hand hygiene-product
Lack of risk perception/knowledge	Improper/inconvenient placement of hand hygiene products	Uncomfortable feeling of hand hygiene product
Attitude towards HH		
Intention for HH (self-protection vs. patient-protection)		
Skin reactions		
Use of gloves		

Stadler RN, Tschudin-Sutter S. What is new with hand hygiene? Curr Opin Infect Dis. 2020 Aug;33(4):327-332.

The main challenge is the suboptimal compliance/adherence by health workers especially in term of non-sustainable improvement, requiring constant encouragement and monitoring. Investing in the promotion of hand hygiene among staff with the introduction of a multimodal program is recommended with the most important elements described as education, reminders, feedback, administrative support and access to alcohol-based hand rub (ABHR) [14-15].

However, some areas are still unclear such as the levels of hand hygiene compliance or of the relative increase necessary to reduce Gram-negative MDRO rates. "Theoretical models suggest that, to interrupt transmission of MDRO in settings where colonization pressure is high, hand hygiene needs

to occur after 60%-80% of patient contacts" [5]. Sickbert and al [16] showed that a 10% improvement in hand hygiene compliance was associated with a 6% reduction in health care–associated infections and that decreases in infection rates have been demonstrated even when improving hand hygiene compliance rates from high (>80%) to very high (>95%). A model by Pelat et al[17], showed that improving HH compliance from 55% before patient contact and 60% after patient contact to 80% before and after patient contact would reduce the proportion of patients who acquire ESBLs within 90 days by 91%.

The WHO program on hand hygiene has set the requirements and offers practical tools for implementation and monitoring. The current SOP builds on those WHO guidelines and other recent implementation recommendations.

Scope

This policy document provides guidance on hand hygiene promotion and best practices to all the participating hospitals in the REVERSE project. The objective of this document is to support the reinforcement of optimal hand hygiene compliance:

- By offering:
  - Tools for the training of healthcare workers
  - Examples of reminders in the work environment
  - Evaluation instruments to monitor compliance and undertake feedback (individual and organisational level)

By proposing:

- the creation of a HH multidisciplinary "improvement group" with medical and nursing staff to analyse critical issues regarding hand hygiene compliance if not already in place
- Improvement in access to ABHR in terms of location and provision with regular monitoring (by point prevalence survey)

Responsibilities

- Infection control team with hand hygiene coordinator /team : implement, encourage, monitor
- Reverse research nurse (which could train link nurses to conduct HH observations)
- Ward nurses, doctors and any person involved in the patient's care
- Patient

General principles and definitions

WHO definitions:

- Alcohol based handrub (ABHR): An alcohol-containing preparation (liquid, gel or foam) designed for application to the hands to reduce the growth of microorganisms. Such preparations may contain one or more types of alcohol with excipients, other active ingredients and humectants.
- Hand hygiene: A general term referring to any action of hand cleansing.
- Handrubbing: Applying an antiseptic handrub to reduce or inhibit the growth of microorganisms without the need for an exogenous source of water and requiring no rinsing or drying with towels or other devices.
- Handwashing: Washing hands with plain or antimicrobial soap and water.

The procedures described below are not differing from the WHO guidelines[18], already in use in many participating hospitals.

HH technique:

The indications for hand hygiene are the five essential moments validated by WHO (""My five Moments for Hand Hygiene" approach) [19], focusing on the contacts occurring within the patient zone during health-care delivery in this area:

Clean their hands (1) before touching a patient, (2) before clean/aseptic procedures, (3) after body fluid exposure/risk, (4) after touching a patient and (5) after touching patient surroundings.

Figure 9: My five moments for hand hygiene



The indications for hand hygiene are independent of those that justify the use of gloves (whether sterile or non-sterile). Glove use neither alters nor replaces the performance of hand hygiene.

The **patient** should also be instructed to perform hand hygiene with alcohol based hand rubs at the beginning of the visit, at the end of the visit and, if applicable, after having been to the toilet.

Techniques:

a) Handrubbing with an alcohol-based formulation

When alcohol-based handrub is available, it is considered as the preferred means for routine hand hygiene if hands are not visibly soiled. ABHR is a cost-effective method to conduct HH, quick, well tolerated, easy to use, independent of water access, and highly effective in reducing microbial load [20]. WHO guidelines consists of 6 steps to ensure an appropriate coverage of both hands with a duration recommended of 20-30 seconds and the use of 3 ml of hand rub.

Figure 9: How to handrub?



However this technique has been challenged in term of timing of alcohol rubbing (for example with 15sec application time in a study by Kramer et al.[21)8]) and number of steps to allow a better compliance of healthcare workers.

The simpler 3-steps technique[22], reported in a Swiss prospective observational study by Tschudin-Sutter et al, shows, following microbiological analyses, a non-inferiority in term of reduction of bacterial counts on the hands of health-care worker. It focusses on the areas of the hands most involved in the pathogens' transmission, with 3 steps (1) covering all surfaces of the hands (based on own judgement), (2) rotationally rubbing the fingertips in the palm of the alternate hand, and (3) rotationally rubbing both thumbs. <u>The simplicity of this technique might confer an enhanced compliance to HH actions.</u>

If these different techniques (15 sec alcohol hand rubbing or 3-steps) have been already put in place in the participating hospital, there is no need to revert to the initial WHO guidance.

b) <u>Hand washing</u>

Hands need to be washed with soap and water when they are visibly dirty or soiled with blood or other body fluids, when exposure to potential spore-forming organisms is strongly suspected or proven, or

after using the lavatory. It requires to apply a correct amount of product to cover all surfaces of hand. The duration recommend of the action is 40-60sec.

Figure 11: How to hand wash?



Remarks

Skin care

Regular and frequent hand hygiene may lead to dryness, chronic changes and damage to skin's microflora. Care of hands is necessary to avoid skin getting dry and chapped. Moreover, microorganisms lodged in broken skin is difficult to remove and can be a source of cross infection. Staff should regularly use hand moisturising agents to reduce irritation and maintain the integrity of the skin.

Jewellery

The consensus recommendation is to discourage strongly the wearing of rings or other jewellery during health care. Wrist watches, bangles, bracelets, wrist bands, rings, false nails, nail products should be removed prior to hand washing. They can be contaminated and can become the means of transmission of infection.

Nails

It is strongly discouraged to use nail polish and recommend to keep nails short and trimmed smooth.

The principle bare-below-the-elbows, either rolled up sleeves or short sleeves, should be encouraged.

Material and Resources

- Alcohol-based handrub should be readily accessible at the point of care (patient zone) – where the risk of cross-contamination and infection transmission is high – either with:
  - staff-carried handrub pocket bottles
  - wall-mounted dispensers
  - Containers affixed to the patient's bed or bedside table or to dressing or medicine trolleys that are taken into the point of care.

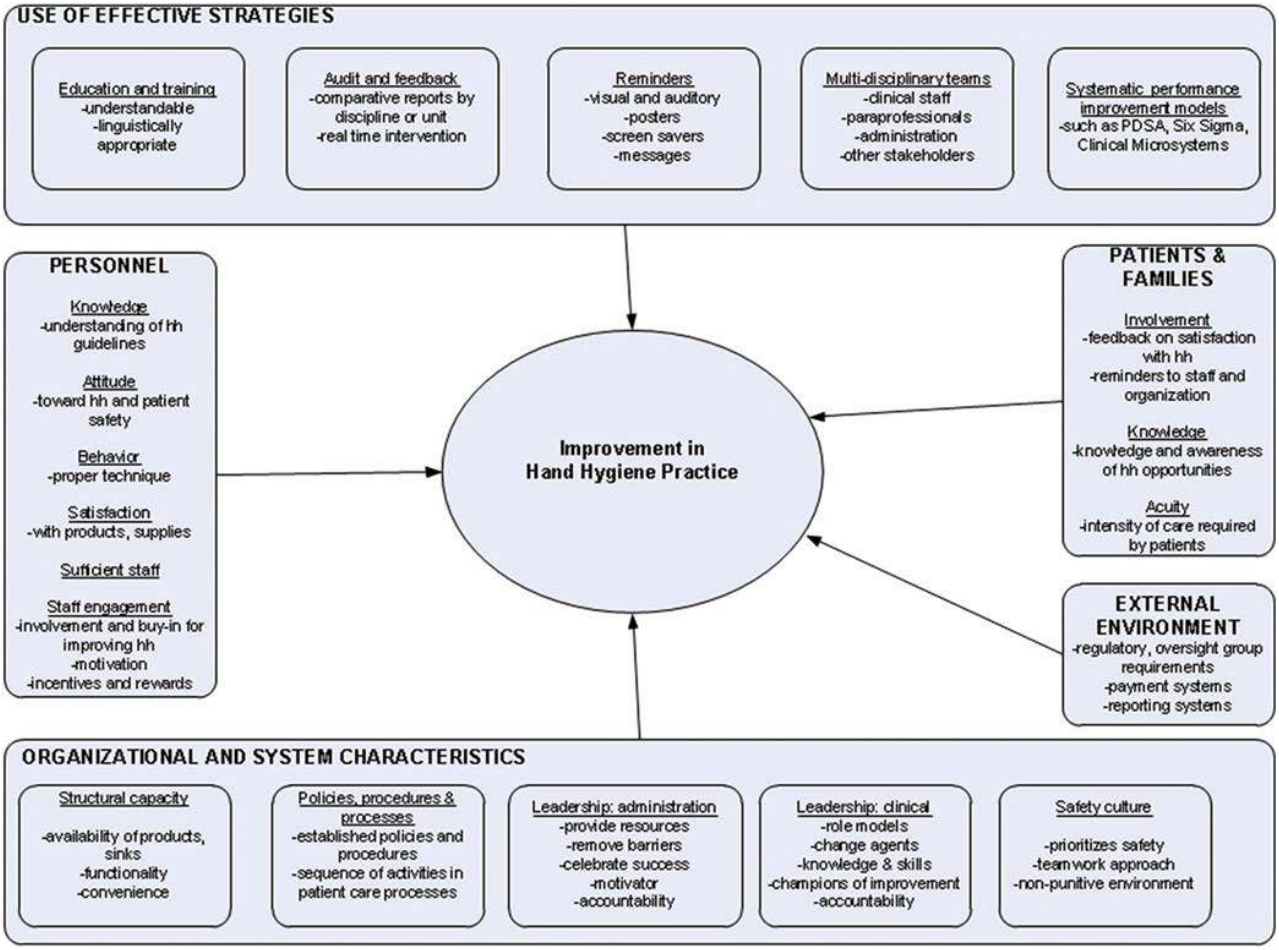
  These supplies should be available in continuous and predictable locations.
  The quality of the alcohol-based product (conformity with European and US standards) need to be checked. (70% alcohol hand rub or gel)

- In case of hand washing, it requires dedicated hand wash basins with soap dispenser, paper towel and a non-healthcare risk waste bin.

Procedures and steps

As described by Pincock et al[23], multimodal strategies are key to improve hand hygiene practice and maintain sustainability as single intervention have shown non lasting improvement. There is a need to work on daily basis to improve hand hygiene standards.

Fig 12: Factors affecting the success of hand hygiene improvement initiatives (reproduced from Pincock et al. 2012)



The key elements of successful hand hygiene promotion are:

a) **Establishing a multidisciplinary team** to evaluate, analyse critical issues regarding hand hygiene compliance and adjust interventions

Tools:

- Baseline evaluation: WHO hand hygiene self-assessment framework 2010- appendix 1
- Support by WP3 for filling the self-assessment framework with exercises during pre-implementation workshop
- WHO template action plan- appendix 2

b) **Appropriate and effective education to health workers**

The training should be regularly/ongoing and it could take place by various means such as:

- Presentations, group discussions, lectures, participation to ward round
- Use of role modelling and mentoring
- Informal education by using opportunities such as medical and nursing rounds, nurse unit meetings, ward "walkabouts".

Tools:

- https://www.who.int/teams/integrated-health-services/infection-prevention-control/hand-hygiene/training-tools
- https://www.cdc.gov/handhygiene/campaign/promotional.html
- TTT by Geneva university hospitals (see below)

c) **Maintain motivation through work place reminders** such as:

- Poster campaigns, pocket cards, brochures
- Recognition of each ward/department's achievements- "ward champions"
- Promotional activities to raise awareness of hand hygiene, such as World Hand Hygiene Day (5th March) or International Infection Prevention Week (October)

Tools:

- https://cdn.who.int/media/docs/default-source/integrated-health-services-(ihs)/infection-prevention-and-control/your-5-moments-for-hand-hygiene-poster.pdf?sfvrsn=83e2fb0e_16
- https://cdn.who.int/media/docs/default-source/patient-safety/how-to-handrub-poster.pdf?sfvrsn=9d2f6e89_11
- Appendix 3 REVERSE HH poster

d) **Adequate access to hand hygiene resources** (ABHR for example)

Tools:

- Hand hygiene product availability audit- Appendix 4
- WHO ward infrastructure survey- appendix 5

e) **Monitoring, evaluation and feedback through**:

- Direct HH observations of the 5 moment's opportunities with individualised verbal performance feedback. Providing real-time feedback on results to the HCWs is a very powerful promotional tool.
- Sharing HH compliance data/reports with hospital unit, during staff meetings for example; Posting compliance results in the wards

Tools:

- https://www.who.int/teams/integrated-health-services/infection-prevention-control/hand-hygiene/monitoring-tools

  - WHO observation form and compliance calculation form- Appendix 6
- TTT for professionals to understand the importance of HH and to monitor it in a qualified manner. It would also enable those professionals to train others HCW.
- https://youtu.be/XZKXMw29kFU

Monitoring, evaluation and feedback

Monitoring performance using hand hygiene compliance is a core measure of every MDRO control program. The direct observation method for WHO's five moments of HH is still considered the gold standard providing qualitative and quantitative information. This method requires trained and validated staff, is time consuming and labour-intensive. There are also potential bias and confounding factors: observation bias (Hawthorne effect), observer bias, and selection bias; hospital ward, time of day/week, patient-to-nurse ratio at time of observation, and type and intensity of patient care.

The compliance with hand hygiene is defined by the ratio of the number of performed actions to the number of opportunities. Noncompliance is when the number of opportunities exceeds the number of actions performed.

Clear principles on the methodology have been defined by WHO such as the observation period (min 10min- max 30min), the number of healthcare workers simultaneously observed (maximum 3), and the requirement to collect data by professional category. There is no clear evidence on the ideal sample size needed to ensure representativeness, but sample size estimates indicate that 200 opportunities [(24)] per observation period and per unit of observation (either ward, department, or professional category etc) are needed to compare results reliably and offer a power to detect difference with two observation periods.

In this project instead of recommending a pre-set goal of compliance rates (benchmark), which will be affected by multiple sources of bias (Hawthorn effect, selection ward….), we would **recommend to target a fixed number of observed opportunities of HH every 6 months.** The compliance rate and a level of increase might reflect adequately the actual improvement in hand hygiene in a unit. It is important to not evaluate too optimistically the situation at baseline, to allow improvement to be observed. **The number of observations per unit (15-20 beds) included in REVERSE would be minimum 3 observation episodes of approximately 20min (min 10min-max 30min) per three months**. The intensity of patient care, estimated by the number of opportunities per hour for each observation period (activity index) will vary between the different wards. However it will allow the observer to spend an equivalent amount of time in each unit, being present and giving feedbacks. There is no maximum observation limit.

The objective is to focus on capturing a diverse large consecutive number of hand-hygiene opportunities and to play back these observations over and over. The goal would be to sustain a compliance rate over time, observing all HCW groups, different shifts/day and realised by different observers, without a fixed compliance benchmark.

Monitoring HH will not only allow to offer feedback individually and institutionally but also is a strong reminder for healthcare workers, sustaining motivation.

Reverse process indicators

REVERSE Protocol data collection:

- **ABHR consumption**, as a surrogate marker for adequacy of hand hygiene.
  The consumption expected for a given hospital depends on the number of opportunities for HH. However consumption does not allow to estimate the HH performance according to actual opportunities and is vulnerable to the influence of unnecessary or obsolete hand hygiene actions.

- Process indicators (point prevalence surveys):
  - Number of observed opportunities quarterly
  - Compliance rate by ward quarterly
  - WHO HHSAF yearly

Process indicators		
Baseline	Year 1	Year 2
WHO hand hygiene self-assessment framework 2010	WHO hand hygiene self-assessment framework yearly	WHO hand hygiene self-assessment framework yearly
Alcohol handrub consumption	Alcohol handrub consumption	Alcohol handrub consumption
	Observed compliance rate quarterly data	Observed compliance rate quarterly data

Appendices:

Appendix 1: WHO HHSAF



WHO-hhsa-framework-october-2010.pd

Appendix 2: WHO template action plan



WHO template-action-plan

Appendix 3: REVERSE HH poster



HH REVERSE poster.pptx

Appendix 4: HH product availability audit



hand_hygiene_product_availability_audi

Appendix 5: WHO ward infrastructure survey



WHO ward-infrastructure-s

Appendix 6: WHO observation form and compliance calculation form



WHO-HH observation-form.doc

References

1. Pittet D, Hugonnet S, Harbarth S, Mourouga P, Sauvan V, Touveneau S, Perneger TV. Effectiveness of a hospital-wide programme to improve compliance with hand hygiene. Infection Control Programme. Lancet. 2000 Oct 14;356(9238):1307-12. doi: 10.1016/s0140-6736(00)02814-2.
2. Allegranzi B, Pittet D. The role of hand hygiene in healthcare-associated infection prevention. J Hosp Infect 2009; Aug 29.
3. Pittet D, Allegranzi B, Sax H, Dharan S, Pessoa-Silva CL, Donaldson L, et al. Evidence-based model for hand transmission during patient care and the role of improved practices. Lancet Infect Dis. 2006;6(10):641–52.
4. Chen YC, Sheng WH, Wang JT, Chang SC, Lin HC, Tien KL, et al. Effectiveness and limitations of hand hygiene promotion on decreasing healthcare-associated infections. PLoS One. 2011;6(11):e27163.
5. Trick WE, Vernon MO, Welbel SF, Demarais P, Hayden MK, Weinstein RA, et al. Multicenter intervention program to increase adherence to hand hygiene recommendations and glove use and to reduce the incidence of antimicrobial resistance. Infect Control Hosp Epidemiol. 2007 Jan;28(1):42-9.
6. Hussein K, Rabino G, Eluk O, Warman S, Reisner S, Geffen Y, Halif L, Paul M. The association between infection control interventions and carbapenem-resistant Enterobacteriaceae incidence in an endemic hospital. J Hosp Infect. 2017 Nov;97(3):218-225. doi: 10.1016/j.jhin.2017.07.018. Epub 2017 Jul 22. PMID: 28743504.
7. Grabowski ME, Kang H, Wells KM, Sifri CD, Mathers AJ, Lobo JM. Provider Role in Transmission of Carbapenem-Resistant Enterobacteriaceae. Infect Control Hosp Epidemiol. 2017 Nov;38(11):1329-1334. doi: 10.1017/ice.2017.216. Epub 2017 Oct 24. PMID: 29061201.
8. Making Healthcare Safer III: A Critical Analysis of Existing and Emerging Patient Safety Practices; AHRQ Publication No. 20-0029-EF March 2020
9. Guidelines for the Prevention and Control of Carbapenem-Resistant Enterobacteriaceae, Acinetobacter baumannii and Pseudomonas aeruginosa in Health Care Facilities. Geneva: World Health Organization; 2017. PMID: 29630191.
10. Tacconelli E *et al*. European Society of Clinical Microbiology. ESCMID guidelines for the management of the infection control measures to reduce transmission of multidrug-resistant Gram-negative bacteria in hospitalized patients. Clin Microbiol Infect. 2014 Jan;20 Suppl 1:1-55. doi: 10.1111/1469-0691.12427.
11. Magiorakos AP *et al.* Infection prevention and control measures and tools for the prevention of entry of carbapenem-resistant Enterobacteriaceae into healthcare settings: guidance from the European Centre for Disease Prevention and Control. Antimicrob Resist Infect Control 6, 113 (2017). https://doi.org/10.1186/s13756-017-0259-z
12. World Health Organisation. Evidence of hand hygiene to reduce transmission and infections by multidrug resistant organisms in health-care settings. Undated.http://www.who.int/gpsc/5may/MDRO_literature-review.pdf. Accessed 04.04.2022
13. Bolton, P., McCulloch, T.J. The evidence supporting WHO recommendations on the promotion of hand hygiene: a critique. BMC Res Notes 11, 899 (2018). https://doi.org/10.1186/s13104-018-4012-3
14. Trick WE, Vernon MO, Welbel SF, Demarais P, Hayden MK, Weinstein RA; Chicago Antimicrobial Resistance Project. Multicenter intervention program to increase adherence to hand hygiene recommendations and glove use and to reduce the incidence of antimicrobial resistance. Infect Control Hosp Epidemiol. 2007 Jan;28(1):42-9. doi: 10.1086/510809
15. Derde LP, Cooper BS, Goossens H, Malhotra-Kumar S, Willems RJ, Gniadkowski M, et al. Interventions to reduce colonisation and transmission of antimicrobial-resistant bacteria in intensive care units: an interrupted time series study and cluster randomised trial. Lancet Infect Dis 2014;14:31–9.

16. Sickbert-Bennett EE, DiBiase LM, Willis TM, Wolak ES, Weber DJ, Rutala WA. Reduction of healthcare-associated infections by exceeding high compliance with hand hygiene practices. Emerg Infect Dis **2016**; 22:1628–30
17. Pelat C, Kardas-Sloma L, Birgand G, et al. Hand hygiene, cohorting, or antibiotic restriction to control outbreaks of multidrug-resistant enterobacteriaceae. Infect Control Hosp Epidemiol 2016; 37(3):272–80.
18. https://www.who.int/publications/i/item/9789241597906 (accessed on 14 April 2022)
19. WHO hand hygiene technical reference manual http://apps.who.int/iris/bitstream/handle/10665/44196/9789241598606_eng.pdf;jsessionid=73E12DD315E2462DF0F8AAEABA570A76?sequence=1(accessed on 14 April 2022)
20. Stadler RN, Tschudin-Sutter S. What is new with hand hygiene? Curr Opin Infect Dis. 2020 Aug;33(4):327-332. doi: 10.1097/QCO.0000000000000654. PMID: 32657970
21. Kramer A, Pittet D, Klasinc R, Krebs S, Koburger T, Fusch C, Assadian O. Shortening the Application Time of Alcohol-Based Hand Rubs to 15 Seconds May Improve the Frequency of Hand Antisepsis Actions in a Neonatal Intensive Care Unit. Infect Control Hosp Epidemiol. 2017 Dec;38(12):1430-1434. doi: 10.1017/ice.2017.217. Epub 2017 Oct 30. PMID: 29081301.
22. Tschudin-Sutter, S., Sepulcri, D., Dangel, M., Schuhmacher, H., & Widmer, A. (2015). Compliance with the World Health Organization Hand Hygiene Technique: A Prospective Observational Study. Infection Control & Hospital Epidemiology, 36(4), 482-483. doi:10.1017/ice.2014.82
23. Pincock T, Bernstein P, Warthman S, Holst E. Bundling hand hygiene interventions and measurement to decrease health care-associated infections. Am J Infect Control. 2012 May;40(4 Suppl 1):S18-27. doi: 10.1016/j.ajic.2012.02.008. PMID: 22546269
24. Sax H, Allegranzi B, Chraïti MN, Boyce J, Larson E, Pittet D. The World Health Organization hand hygiene observation method. Am J Infect Control. 2009 Dec;37(10):827–34

Contact precautions

Title	Contact precautions
Document status	Approved by on
Version Number	V1
Authors	Vered Schechner, Yehuda Carmeli

Introduction

Horizontal transmission of multi drug-resistant gram-negative bacteria (MDR-GNB) in healthcare facilities occurs via direct and indirect contact. The main mode of transmission of MDR-GNB is by indirect contact and is mediated by contaminated intermediate vectors, such as the hands of healthcare personnel, shared medical equipment and devices, and the medical environment. Direct transmission of MDR-GNB between patients is uncommon, but may occur during medical procedures that cause a spray of droplets that can reach other patients.

Contact precautions (C/P) are measures recommended in addition to standard precautions in order to prevent the spread of resistant pathogens between patients. These measures include: (1) separation of patient by appropriate placement; (2) limiting transport and movement of patients; (3) use of personal protective equipment, including gloves and gowns to limit contamination of healthcare personnel; (4) use of disposable or dedicated patient care equipment or the cleaning of these devices after patient contact; and (5) enhanced cleaning and disinfection of patient rooms.[1]

MDR-GNB are among the target pathogens for implementation of C/P, and C/P have been demonstrated to be effective during outbreaks of MDR-GNB[2,3]. The target MDR-GNB for which C/P are recommended may vary between facilities and within facilities (differing by unit). Studies observing the rates of compliance with C/P have shown varied results, depending on the location (i.e., ICU), type of healthcare workers, and the prevalence of patients for which C/P are required.[4,5] Furthermore, the duration of C/P is not well defined and may vary between target pathogens.[6] Even for CPE, for which some countries have policies for discontinuing isolation, these policies are based on observational studies and cumulative experience.

Scope

This policy document provides guidance on C/P to all the participating hospitals in the Reverse project. The objective of this document is to support the implementation of C/P.

By offering:

- Guidance on which patients require contact precaution
- Guidance on how to implement C/P
- Training tools, including demonstrations of donning and removing PPE
- Tools to monitor adherence to C/P
- Information sheets for patients and families regarding C/P

By proposing:

- A daily list of patients who need to be under C/P (and the organism name) sent to ward heads and hospital management
- Computer pop-up alerts stating that a patient requires C/P, in all patient care areas in the hospital

General principles/information and definitions

Definitions:

- MDR-GNB – CRE, CRAB, CRPsA
- CPE – CRE which has been confirmed as carrying a carbapenemase gene, or having a carbapenem hydrolysis phenotype
- MDR-GNB Carrier - A patient from whom an MDR-GNB was isolated, by either surveillance or clinical samples
- Horizontal preventive measures – standardized practices to prevent horizontal transmission that do not depend on patient-specific carriage status (e.g., hand hygiene, standard precautions, environmental cleaning and disinfection).
- Patient bay - the patient's immediate environment dedicated solely to the individual patient. The patient bay includes the patient bed, chair, table, or other device that supports the patient during examination and treatment, and the area surrounding them (typically 1.8 m).
- Personal protective equipment (PPE) – specialized clothing or equipment worn by a HCW for protection against infectious materials. PPE may include: gowns, gloves, masks, head covers, eye protection.
- Pre-emptive C/P –C/P for patients at high risk of MDR-GNR carriage (e.g. outbreak setting) that are applied before screening culture results become available.
- Activities of daily living (ADL) – basic self-care tasks (e.g., bathing, personal and toilet hygiene)

General principles:

- C/P should be applied in addition to horizontal preventive measures (i.e., in addition to hand hygiene and standard precautions).
- C/P should be applied by all healthcare personnel at all hospital treatment sites

Which patients require C/P?

- All MDR-GNB carriers should be placed under C/P. C/P should be applied irrespectively if colonized or infected.
- C/P should be applied to all carriers: carriers isolated in a single room or cohorted with carriers of a specific MDR-GNB, or hospitalized in the same room with other patients (non-carriers or carriers of a different MDRO).

How to apply C/P

(i) Appropriate patient placement

- It is recommended to isolate a patient under C/P in a separate room (that includes a toilet and a bathroom) or together with other carriers of a specific MDR-GNB (i.e. cohorting). See the "isolation and cohorting" SOP.
- Patient placement in a multi-patient room with other patients (non-carriers or carriers of a different MDRO) can lead to cross-transmission.
- If hospitalization in a multi-patient room is unavoidable, the bay of a patient under contact precaution should preferably be located at the back of the room and physically separated from other patients' bays in the same room (ideally by using a fixed, rigid and washable partition). If the patient bay is narrow or overcrowded by medical equipment, the adjacent bay should remain empty to avoid transmission.
- Ventilated patients who are carriers of CRAB or CRPsA have higher risk of direct transmission by droplet spray. Therefore their separation by placement should be prioritized.
- Special attention should be given to accommodate the needs of patients independent in ADL while maintaining C/P, and specifically to use separate toilet and bathroom.

(ii) Limiting transport and movement of patients

- The movement of patients under C/P within the hospital should be restricted to essential purposes only.
- The orderly who is moving the patient and the unit to which the patient is being transferred must be informed about the MDR-GNB carriage, and apply C/P measures
- Patients under C/P and their families and visitors should be instructed to stay in the patient's station. If a patient must leave the room (e.g., for smoking), a plan must be made (where, when, how) to avoid transmission.

(iii) Use of personal protective equipment

- A patient isolation room (or bay in a multi-patient room) should be clearly marked by a sign. The medical chart should also be flagged.
- All healthcare personnel should don gowns and gloves upon entrance to the patient room/bay, even if no direct contact with the patient is planned.
- HCWs should don PPE immediately before entrance to the patient bay, and remove it before leaving the patient bay.
- Leaving the patient room (or bay) while still wearing PPE is prohibited!
- The PPE storage and donning area should be defined (outside the patient bay)
- PPE removing area should be defined (inside the patient bay, close to the exit of the bay or room)
- Clean gloves should be available in the patient's bay and replaced during the patient's treatment according to hand hygiene guidelines.
- Hand hygiene should be performed before donning gloves and after removing gloves.
- If carriers are brought to a treatment area (e.g., CT scan), HCWs there must use PPE according to the same principles (donning gloves and gowns before approaching the patient and removing them before leaving the area).

(iv) Allocation of patient care equipment

- Use disposable or dedicated patient care equipment for everyday use (e.g., blood-pressure cuff, stethoscope, glucometer, arm chair) for each patient under contact precautions. The allocated patient care equipment should be placed within the patient bay.
- Medical devices that are used both by patients under C/P and others (e.g., X-ray machine, ECG) should be cleaned and disinfected after use for patients on C/P (and then moved out of the C/P area).

(V) Enhanced cleaning and disinfection of patient rooms.

- See SOP regarding routine and terminal cleaning

Duration of C/P:

- Carriage of MDR-GNR often continues for several months.
- For the specific admission in which carriage of the MDR-GNR was detected, C/P should be continued for the entire duration of hospital stay.
- On readmissions, C/P should be applied according to the time elapsed since the last detection of the MDR-GNR. We recommend implementing C/P if a carrier is readmitted within 3 months from the last detection of MDR-GNB. For readmissions >3 months from the last detection of the MDR-GNR, C/P should be applied until at least 2 consecutive screening cultures and cultures from relevant clinical sites are negative without effective antibiotherapy.

Procedures and steps

1. Define criteria for implementing C/P

- Decide how to handle known carriers on readmissions
- Decide who should be treated by preemptive C/P
- Decide how to handle suspected carriage of resistant bacteria
- Define a process for determining if carriers have achieved clearance (i.e., are no longer colonized)

2. Build a process for early identification of patients who need to be under C/P

- Monitor clinical samples for the target pathogens
- Implement active screening of high risk groups upon admission and during hospitalization
- Create a system for direct rapid reporting from the lab
- Create an alert system to identify known carriers on readmission and on ward transfer.

3. Monitor the census of patients under C/P

- Construct daily reports of all carriers/infected patients according to pathogens, wards, rooms and isolation status

5. Define how to manage patients under C/P

- Create a checklist of actions to be done upon notice of a new MDR-GNB carrier (e.g., define what is the best location for the patient, mark the patient bay with a sign, organize the PPE doffing and donning area, organize the dedicated equipment, mark the patient chart)
- Instruct staff
- Make information sheets for patients and visitors

6. Monitor adherence to guidelines and give feedback

- Construct reports of adherence to C/P. Share compliance data with hospital units and management
- Perform audits of C/P compliance. Give feedback.

Responsibilities

Microbiology laboratory – Identify and report positive (or suspicious) samples for MDR-GNR

Ward staff– adherence to C/P rules, instructions to patients/families

Patients/families – adherence to C/P rules

IPC team – making all the local guidelines on how this hospital will implement C/P, instructing all the staff, monitor adherence to C/P rules, give feedback, report

Administration/informatics - supply of equipment, daily census of carriers who need to be under C/P

Reverse WP3 – Support the local IPC team

Materials and Resources

A daily list of patients requiring C/P in each ward

Information sheets for patients and families (available in the outbreak investigation SOP)

Check list for staff - patient isolation design

Monitoring and Evaluation

Process indicators:

- % of patients requiring C/P who are actually under C/P (by ward)
- % compliance – infrastructure, placement and equipment
- % compliance – staff behavior

Appendices

Tools:

- *Appendix 1:Description of patient isolation design (in a multi-patient room) and a checklist*
- *Appendix 2: Audit tool to monitor adherence to C/P*
- *Appendix 3:An example of a daily census of patients under C/P*

References:

1 World Health Organization. Guidelines for the Prevention and Control of Carbapenem-Resistant Enterobacteriaceae, Acinetobacter baumannii and Pseudomonas aeruginosa in Health Care Facilities. 2017.

2 Siegel JD, Rhinehart E, Jackson M, Chiarello L and the HICPAC. Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Healthcare Settings. 2007. http://www.cdc.gov/ncidod/dhqp/pdf/isolation2007.pdf.

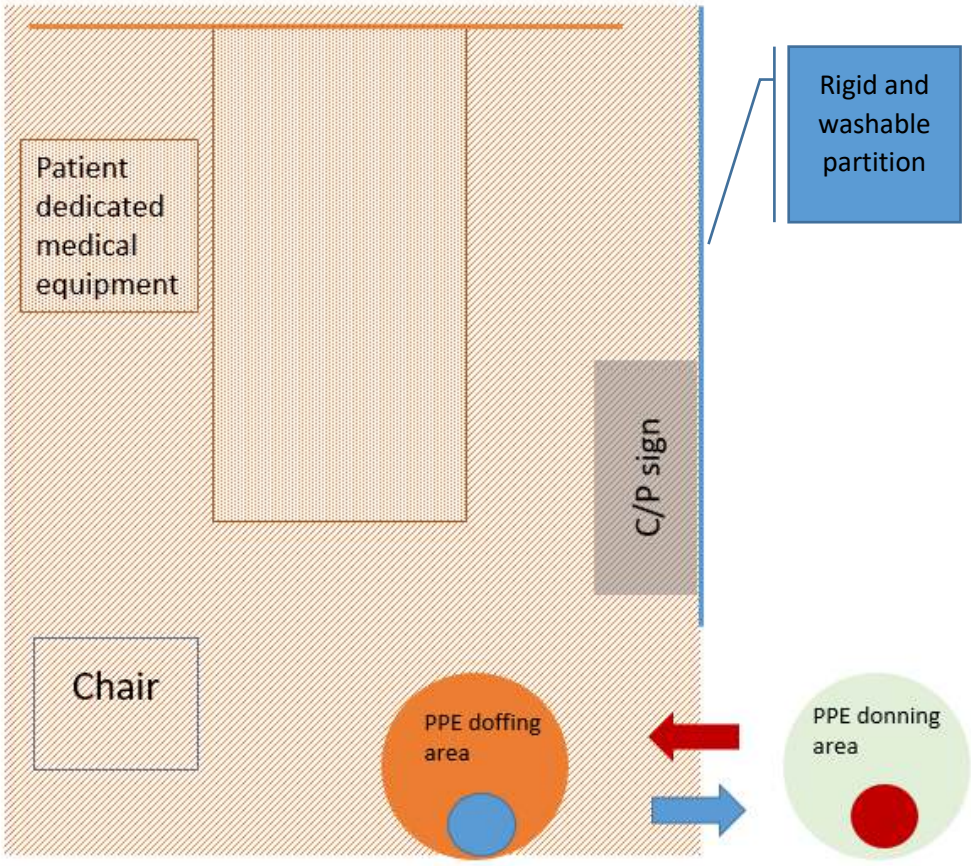
3 Landelle C, Pagani L, Harbarth S. Is patient isolation the single most important measure to prevent the spread of multidrug-resistant pathogens? *Virulence* 2013; **4**: 163–71.

4 Dhar S, Marchaim D, Tansek R, *et al.* Contact precautions: more is not necessarily better. *Infect Control Hosp Epidemiol* 2014; **35**: 213–21.

5 Clock SA, Cohen B, Behta M, Ross B, Larson EL. Contact precautions for multidrug-resistant organisms: Current recommendations and actual practice. *Am J Infect Control* 2010; **38**: 105–11.

6 Banach DB, Bearman G, Barnden M, *et al.* Duration of Contact Precautions for Acute-Care Settings. *Infect Control Hosp Epidemiol* 2018; **39**: 127–44.

Appendix 1: Description of patient isolation design (in a multi-patient room) and a checklist



Checklist :

- ☐ Separated from other patients (preferably by a rigid partition)
- ☐ Clear C/P sign
- ☐ PPE donning area:
  - ☐ outside patient station
  - ☐ contains gloves, gowns, and alcohol-based hand rub
- ☐ PPE doffing area
  - ☐ before the exit from patient station
  - ☐ contains a trash container with lid and foot pedal, alcohol-based hand rub
- ☐ Dedicated medical equipment – located inside patient bay

Appendix 2: Technical audit tool – adherence to C/P

Name of facility:
Department: Unit:
Date of audit:
Week day:
Shift:
Person responsible for audit:

1. Direct observation – infrastructure, placement and equipment

Evaluate the infrastructure, placement, and equipment for patients under C/P:

Element	Patient #1	Patient #2	Patient #3	Patient #4
C/P marked in chart				
Patient placement is as recommended				
In a multi-patient room, the patient bay is physically separated from other patients' bays				
The patient bay (or room) is clearly marked by a C/P sign				
PPE donning area located outside patient bay				
PPE donning area contains gloves, gowns, and alcohol-based hand rub				
PPE doffing area is located immediately before the exit from the patient bay (or room)				
PPE doffing area is separated from PPE donning area				
PPE doffing area contains a trash container with lid and foot pedal, and alcohol-based hand rub				
Dedicated patient care equipment is allocated as required				
Dedicated patient care equipment is located inside patient bay (or room)				

A: satisfactory
B: partially meets requirements
C: does not meet requirements

2. Direct observation and questioning – behaviour

Evaluate the patient and staff behaviour:

Element	Patient #1	Patient #2	Patient #3	Patient #4
Patient was instructed about C/P rules				
Patient is in the bay (unless indicated to move to another treatment area)				
Visitors use PPE as required				
HCW use PPE as required				
HCW remove PPE before exit from the patient bay				

A: satisfactory
B: partially meets requirements
C: does not meet requirements

Feedback:

- ☐ Yes
- ☐ No

Appendix 3: An example of a daily census of patients under C/P

Summary daily census – DD/MM/YYYY

Department	# of carriers of MDR-GNB	# of carriers of CPE	# of carriers of non-CP CRE	# of carriers of CRAB	# of carriers of CRPsA
Int Med A	5	1		3	1 *
Int Med B	2		1		1
Surgery A	3	2 *	0	1	
Surgery B	0				
General ICU	3			3	2
Total	**13**	**1**	**1**	**7**	**3**

** New in the report*

Detailed daily census DD/MM/YYYY

Patient				Placement			MDR-GNR carriage					Other MDR carriage	C/P Charting
Name	Sex	ID	Age	Department	Room number	Bay number	CPE	CPE carbapenemase (specify)	Non-CP CRE	CRAB	CRPsA	Other MDR (specify)	C/P is labeled in chart
xxxx	M	12345	56	Int Med A	3	1				√		MRSA	√
yyyy	M	23456	82	Int Med A	3	2			√	√*			√
zzzz	F	34567	73	Int Med A	2	1	√	KPC				MRSA	√
kkkk	F	45678	58	Int Med B	3	1				√			No

* *New in the report*

Isolation and cohorting

Title	Isolation and cohorting
Document status	Approved by on
Version Number	V1
Authors	Vered Schechner, Yehuda Carmeli

Introduction

Territorial separation is an effective mean of preventing cross-transmission. Carriers of multidrug-resistant organisms (MDROs) serve as a reservoir and may contaminate the nearby environment. Physical separation of carriers helps to prevent contact with other patients and to confine the contaminated environment in which contact precautions are required. In addition, territorial separation makes it easier to carry out contact precautions (i.e., the need to don gown and gloves when entering the patient area and use of dedicated equipment), and it clearly defines the area in which PPE should be donned or removed and hand hygiene performed.[1]
The WHO describes two ways to separate carriers from non-carriers during hospitalization. 1) Isolation, defined as placement in a single room (preferably with its own toilet facilities); 2) Cohorting, defined as grouping together patients who are colonized/infected with the same resistant organism in one area. While the former is considered the preferred option, as it allows continuation of care in the same ward, cohorting may be more effective in preventing the spread of MDR-GNB. Cohorting may be required when there is a shortage of single-patient rooms, allowing for more efficient use of hospital rooms and resources.[2]

An additional effective measure is staff cohorting, i.e. use of dedicated staff to exclusively manage isolated/cohorted patients. This measure is highly effective in preventing cross-transmission, but its feasibility may be challenging for certain professions and during certain shifts. Therefore, staff cohorting usually includes only some professions (usually those with prolonged close contact with patients) and in other professions may be adopted only during certain shifts. Patient cohorting increases the feasibility of staff cohorting.

Although the rationale for isolation and cohorting (I/C) is clear, there are still gaps in the knowledge and supporting evidence for the real-world effectiveness of implementing I/C for carriers of MDR-GNB. These gaps include:

1. Data on the effectiveness of I/C are based mostly on CRE/CPE patients. While the same rationale applies for other organisms, transmission dynamics may differ between the three groups of pathogens.
2. Effectiveness and feasibility of I/C in endemic settings may differ from outbreak situations.
3. Interventions to reduce MDROs transmission are usually multifaceted, and studies lacked the ability to measure the contribution of each component by itself.[3–5]

Conflicting data exist regarding the possible adverse effects of I/C, including waste of resources (e.g., unoccupied beds in multi-patient rooms), potential harm to patient clinical care and well-being, and staff burnout.[6,7] Nevertheless, I/C remains a mainstay of targeted interventions to prevent transmission of MDROs.

Scope

This policy document provides guidance on patient I/C to all the participating hospitals in the Reverse project. The objective of this document is to support the implementation of I/C in both outbreak situations and endemic settings.

By offering:

- Guidance on how to implement I/C in different settings.
- Instructions on how to manage infection prevention and control (IPC) in cohort units.
- Tools to monitor adherence to I/C rules.
- Tools to identify and monitor lapses in I/C practices (i.e., failure of containment or within-cohort cross-transmission).

By proposing:

- An algorithm to determine which patients should be placed in private isolation rooms or in a cohort.
- Centralized management of all patient in I/C.
- Daily reporting of I/C status for colonized/infected patients.
- Audits to measure compliance with IPC guidelines
- Information sheets for patients and visitors.

General principles/information and definitions

Definitions:

- Isolation – colonized/infected patients are placed in single-patient rooms (preferably with their own toilet facilities)
- Cohorting – grouping together patients who are colonized/infected with the same organism to confine their care to one area and prevent contact with other patients.
- Staff cohorting – dedicating staff to care only for the isolated/cohorted patients
- Failure of containment – an event of probable transmission from a patient within the cohort to a patient outside the cohort unit but within the same ward.
- Within-cohort cross-transmission – transmission of a different resistant pathogen (or a different carbapenemase) between patients in the same cohort unit.

General principles:

- Patient I/C does not replace contact precautions and horizontal preventive measures. I/C adds another layer of protection.
- Patient cohorting is reserved for situations where there are insufficient single rooms or where cohorting of patients colonized or infected with the same pathogen is a more efficient use of hospital rooms and resources. Patient cohorting should also be used when single room isolation has failed to limit the spread of MDROs.
- Staff cohorting can strengthen the impact of patient cohorting.
- There must be a separate cohort for each group of resistant pathogens (i.e., CPE, CRAB, and CRPsA). Do not use one general cohort for all MDROs carriers.
- If feasible, within a CPE cohort, patients with different carbapenemases (if known) should be placed in separate rooms.
- If a carrier has more than one target pathogen, isolation in a single-bed room is preferred. If it is impossible, priority should be pre-defined. (For example, if a patient is a carrier of CPE and CRAB, have a rule about whether such patients should be placed in the CPE cohort or the CRAB cohort).

- To limit patients leaving the cohort area, consultations and diagnostics tests (e.g., X-ray) should preferably be performed in the cohort area.
- If the patient's clinical condition does not allow hospitalization in a cohort area, the patient should be placed in an isolation room where care is appropriate for the condition. The isolation rules in this area should not be inferior to those of the cohort.

How to design a cohort

(i) Cohort area:

- Carriers should be placed in an area that is physically defined and separate from areas where there is activity and movement of non-cohort patients**.**
- The cohort area should be clearly marked by a sign.
- The cohort area should have an anteroom, or a marked transition area.
- If more than one room is necessary, the rooms should be next to each other, ideally in a separated area towards the back of the ward.
- While the cohort area may change its size based on daily occupancy, it is recommended not to change the area often, even if some beds are left empty. Each area change increases the risk of transmission, due to environmental contamination or less than optimal cohort area conditions.

(ii) Equipment:

- Assign dedicated equipment for the cohort (e.g., sphygmomanometer, stethoscopes, ECG device, medical computer cart etc.)
- Equipment that needs to be moved in and out of the cohort area (e.g., X-ray machine, ultrasound device) should be thoroughly cleaned and disinfected before it is removed from the cohort area.
- All equipment in the cohort must be washable. For example, use washable keyboards and replace torn mattresses.

(iii) Staff:

- On each shift, the staff members (medical and non-medical) who take care of the cohort patients and the cohort area should be chosen. The number should be limited to the minimum that is required. For example, if there are 2 patients in a cohort, the same nurse should be assigned to both of them.
- If you choose to cohort staff, staff cohorting usually includes only some of the HCWs providing care and services in the cohort unit. Usually the nurses and nurse aides are cohorted, while physicians, cleaning personnel, consultants and various technicians are not dedicated to the cohort only, but have limited access to the cohort unit.

(iv) Entry and exit:

- Patients may leave the cohort area only accompanied by a staff member and to a defined site (e.g., operating room, MRI). Prior to the transfer, arrival and necessary precautions must be coordinated with the site to which the patient is being transferred.
- The number of times that staff enter and exit the cohort should be kept to a minimum. Organize workflow to do as many tasks as possible in the same visit. For instance, the physician who examines the patients should take blood tests during the same visit; the nurse who takes vital signs should give medication during the same visit.
- Staff who are treating both cohort and non-cohort patients on the same shift should enter the cohort last (if possible). This will limit the risk of cross-transmission.
- Staff who are treating only the cohort patients should have predefined rules for leaving the cohort area for rest breaks and going to other essential sites in the ward outside the cohort area.

- Removal of dirty laundry and trash from the cohort area should be coordinated. Use either direct removal from the cohort area (e.g. through a shaft) or a double bag (i.e., the outside bag should come from the clean area).

(v) Visitors

- Family and visitors' entry to the cohort area should be controlled. While visiting patients is important for the patient and family, it may carry a risk of transmission. Thus, visitors should be allowed to visit the cohort unit, but this should be controlled and supervised to prevent overcrowding.
- Visitors should be instructed on behaviour and infection control measures inside the cohort unit, and be advised not to visit other areas of the ward/hospital after visiting the cohort unit. It is advised that visitors use gowns and gloves on entry to the cohort unit. They should follow the same procedures for donning and doffing as HCWs.

(vi) Cleaning

- Use dedicated cleaning equipment for the cohort area (i.e., cleaning cart and mop). Store this equipment in the cohort area.
- Apply enhanced cleaning and disinfection of the cohort area (see SOP)

Instructions for staff in the cohort:

- Before entrance to the cohort area: don a designated cohort uniform and don a single-use gown (within the anteroom)
- Do not bring in personal equipment (i.e., cell phones, pens and pencils)
- Use personal protective equipment as specified in the Contact Precautions SOP
- When moving between patients in the cohort, remove gloves and perform hand hygiene. Gowns should be changed if soiled or if patients do not have the same MDRO (e.g., in the CPE cohort, change your gown if your first patient carries CPE and CRAB and the next patient carries only CPE).
- Before leaving the cohort area: remove gown and perform hand hygiene before going to the anteroom.
- Staff who leave the cohort just for a break should either remove and exchange their uniform, or cover their uniform with a clean gown before leaving the anteroom.
- See Appendix 1 for the organization of the cohort area

Procedures and steps

1. Define criteria for implementing I/C

- Each hospital should have predefined criteria for which patients require I/C and who can be part of the same cohort.
- Address each specific group of pathogens
- Address the specific I/C strategy applied in different settings (for example, cohorting carriers of a resistant pathogen at the level of a ward or wing or hospital; cohorting CRAB carriers only if they are in the ICU or on a ventilator)

2. Build a process for early identification of patients who need to be under I/C

- Monitor clinical samples for the target pathogens
- Perform active screening of high risk groups upon admission and during hospitalization
- Implement direct rapid reporting from the lab
- Create an alert system to identify known carriers on readmission and on ward transfer.

3. Define a coordination team for patients who need to be under I/C

- Define who in the coordination team must approve transfer of patients to a cohort (to avoid mistakes) or hospitalization of carriers outside a cohort
- Construct daily reports of all carriers/infected patients according to pathogens, wards, rooms and isolation status
- Set criteria for I/C (e.g., who can be in a cohort together; what cohort should be used for patients with two different resistant pathogens)
- Define a process for determining if carriers have achieved clearance (i.e., are no longer colonized)

5. Define how to manage patients under I/C

- Create protocols for the routine workflow of patients under I/C (e.g., dedicated equipment, staff entering and leaving I/C units, staff moving between patients within a cohort (in the same room and between rooms), transfer of a patient under I/C to a procedure/treatment outside the I/C unit, routine cleaning, terminal cleaning, garbage disposal)
- Instruct staff
- Create information sheets for patients and visitors

6. Monitor adherence to guidelines and give feedback

- Construct reports of adherence to I/C. Share compliance data with hospital units and management
- Perform audits of IPC practices in the cohorts. Give feedback.
- Investigate events of failure of containment or within-cohort cross-transmission. Share your findings with the management and the staff of the ward in which the cohort is placed.

Responsibilities

- I/C coordinator + infection control team: central coordination of I/C, monitor adherence to I/C.
- Infection control team: write guidelines, perform audits, monitor outcome and process measurements
- Ward nurses, doctors and any person involved in the patient's care: follow guidelines for care of patients and use of PPE in I/C
- Patient/visitors – follow I/C guidelines

Material and Resources

Room or group of rooms dedicated for patients under I/C

Dedicated staff area which allows the staff to conduct their required activity without leaving the cohort area

Dedicated equipment for patients under I/C

Microbiology laboratory support – rapid identification of carriers and notification to wards

Coordination and rapid response team with authority to transfer patients into the I/C area

Monitoring and Evaluation

1. % adherence to patient I/C
   - Instructions: perform 4 (?) point prevalence audits per month (see table 1)
   - % of patients requiring I/C who are actually under I/C (according to the hospital's own policy of who requires I/C):

- *Target:* 90%

2. Speed of isolating or cohorting newly identified MDR-GNB carriers

- Instructions: perform a point prevalence audit of 10 patients in a cohort per month (see table 2)
- *Time from laboratory result of a positive sample for MDR-GNR to initiation of I/C (hours)*
- *Target: set up target preferably within 4h and no longer than 24h*

3. Failure of containment = detection of the target resistant pathogens in patients outside the cohort (indicating probable transmission from the cohort) per 100 I/C days

- Instructions: calculate monthly for each cohort (see table 3).
- Number of detections outside the cohort * 100
  Number of cohorted patient days (per month)
- *Target: 0*

4. Within-cohort cross-transmission (defined as probable transmissions of a different resistant pathogen or a different carbapenemase between patients in the same cohort unit (per 100 I/C days)

- Instructions: calculate monthly per each cohort (see table 3)
- Number of transmissions within the cohort * 100
  Number of cohorted patient days (per month)
- *Target: 0*

Appendices

- *Appendix 1: Description of a CPE cohort area*
- *Appendix 2: Technical tools for I/C*

References:

1 Tacconelli E, Cataldo MA, Dancer SJ, *et al.* ESCMID guidelines for the management of the infection control measures to reduce transmission of multidrug-resistant Gram-negative bacteria in hospitalized patients. *Clin Microbiol Infect* 2014; **20 Suppl 1**: 1–55.

2 World Health Organization. Guidelines for the Prevention and Control of Carbapenem-Resistant Enterobacteriaceae, Acinetobacter baumannii and Pseudomonas aeruginosa in Health Care Facilities. 2017.

3 Abad CL, Barker AK, Safdar N. A systematic review of the effectiveness of cohorting to reduce transmission of healthcare-associated C. difficile and multidrug-resistant organisms. *Infect Control Hosp Epidemiol* 2020; **41**: 691–709.

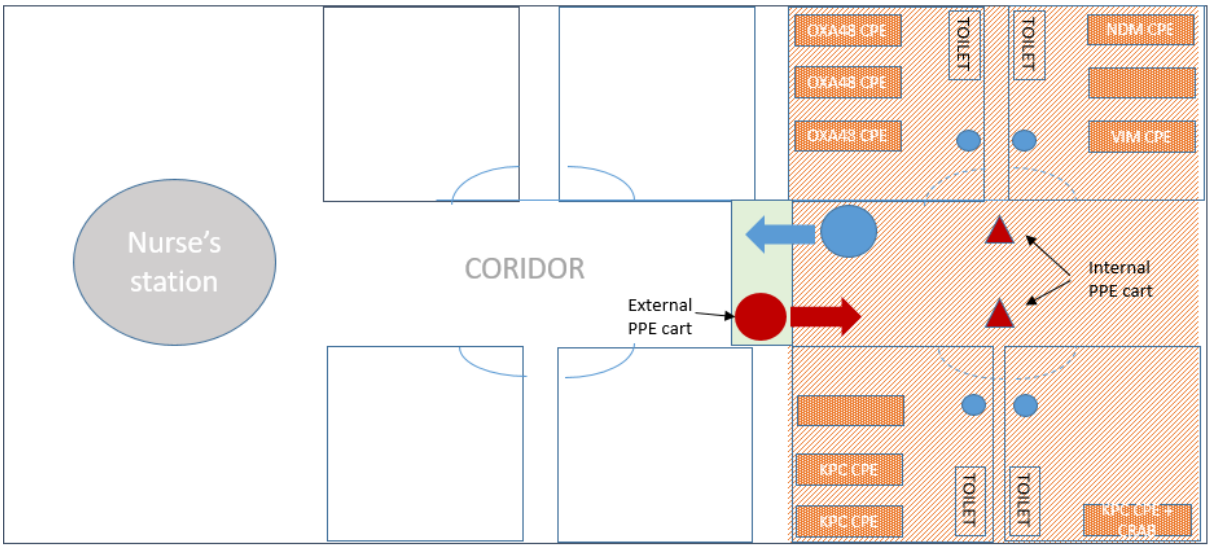
4 Arruda MC, de Aguiar RS, Jardim WM, *et al.* Cohorting to prevent acquisition of multidrug-resistant bacteria: An interrupted time series study. *Am J Infect Control* 2019; **47**: 180–5.

5 Hilliquin D, Lomont A, Zahar J-R. Cohorting for preventing the nosocomial spread of Carbapenemase-Producing Enterobacterales, in non-epidemic settings: is it mandatory? *J Hosp Infect* 2020; published online April 18. DOI:10.1016/j.jhin.2020.04.022.

6 Saliba R, Karam-Sarkis D, Zahar J-R, Glélé LSA. Adverse events associated with patient isolation: a systematic literature review and meta-analysis. *J Hosp Infect* 2022; **119**: 54–63.

7 Eli M, Maman-Naor K, Feder-Bubis P, Nativ R, Borer A, Livshiz-Riven I. Perceptions of patients' and healthcare workers' experiences in cohort isolation units: a qualitative study. *J Hosp Infect* 2020; **106**: 43–52.

Appendix 1: Example of a cohort area (CPE)



Description of a CPE cohort area:

- ✓ The cohort area (orange) includes 4 adjacent rooms at the back of the ward
- ✓ Patients are grouped by carbapenemase type (if possible)
- ✓ A carrier of both CPE and another MDR-GNB is located in a separate room.
- ✓ The anteroom to the cohort area (green) is the PPE donning area
    - o A cart with PPE (External PPE cart (red circle) – with the designated cohort uniforms, gloves, gowns, alcohol hand rub) is located in the anteroom
    - o Carts with PPE (Internal PPE carts (red triangles) – with gowns, gloves, alcohol hand rub) are located near the entrance to the patient rooms, for use inside the cohort area. It is also possible to put the cart inside the patient room, if it is far from the patient station
- ✓ PPE doffing area (blue circle) is located before exit from each patient's room and also before exit from the cohort area
    - o Include trash container with lid and foot pedal and alcohol-based hand rub or a sink with soap and towel?

Appendix 2: Technical tools for I/C

Table 1. Tools to monitor I/C compliance (fill in the grey boxes, see example)

Year		2023			
Month		March			
		Audit#1	**Audit#2**	**Audit#3**	**Audit#4**
Date					
CPE	# of CPE carriers	13	13		
	# of CPE carriers in I/C*	10	13		
	% compliance to CPE I/C (per audit)	77%	100%		
	Total CPE compliance (per month)				88%
CRAB	# of CRAB carriers	6	4		
	# of CRAB carriers in I/C*	5	4		
	% compliance to CRAB I/C (per audit)	83%	100%		
	Total CRAB compliance (per month)				92%
CRPsA	# of CRPsA carriers	12	12		
	# of CRPsA carriers in I/C*	12	12		
	% compliance to CRPsA I/C (per audit)	100%	100%		
	Total CRPsA compliance (per month)				100%
MDR-GNR	# of MDR-GNR carriers	28	29		
	# of MDR-GNR carriers in I/C*	26	29		
	% compliance to MDR-GNR I/C (per audit)	93%	100%		
	Total MDR-GNR compliance (per month)				96%

* According to the hospital policy of I/C

Table 2. Tools to monitor time to implementation of I/C (fill in the grey boxes)

Name of the cohort			
Date			
Department			
Auditor			
Patient number	**Initial positive sample result (insert date/hour)**	**Patient placed in isolation or cohort (insert date/hour)**	**Time to implementation of I/C (calculate time difference, in hours)**
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			

Table 3. Tools to monitor lapses in I/C (fill in the grey boxes, see example)

Year	2023
Month	March
Name of the cohort	CPE
Department	Internal medicine A
Number of detections outside the cohort (per month)	3
Number of transmissions within the cohort (per month)	2
Number of cohorted patient days (per month)	103
Failure of containment (per 100 isolation days)	2.9 (3/103*100)
Within cohort cross-transmission (per 100 isolation days)	1.9 (2/103*100)

Manual for MDRO screening

Title	Manual for MDRO screening
Document status	Approved by on
Version Number	1
Authors	Alberto Antonelli, Marco Coppi, Chiara Bonaiuto, Ilaria Baccani, Tommaso Giani, Gian Maria Rossolini

Introduction

One of the most important challenges of modern medicine is represented by infections caused by multidrug resistant bacteria (MDRO). The recent spread of resistant organisms has led to an increasing impact of disease severity and mortality due to the scarcity of effective therapies. Infections caused by carbapenem-resistant Gram-negatives (CR-GN), including Enterobacterales and Gram-negative non-fermenters, are especially challenging.

Moreover, infections by CR-GN represent only the tip of the iceberg compared to the number of colonized patients who are the major source for cross-transmission of these pathogens. The main reservoir for enterobacteria is the intestinal tract, while *Pseudomonas* and *Acinetobacter* more frequently colonize skin and upper respiratory airways (1-3). An increasing number of studies underscored the importance of active surveillance to detect carbapenem-resistant *Enterobacterales* (CRE) at admission and during hospitalization to limit their spread by infection control practices and also inform about prophylaxis measures in case of surgery and empiric treatments in immunocompromised patients. On the other hand, the importance of screening for carbapenem-resistant *Acinetobacter* and *Pseudomonas aeruginosa* is still debated (CRAB and CRPsA, respectively) (4-6). Reduced evidence has been underscored for extended-spectrum β-lactamase-producing *Enterobacterales* (ESBL), even if their screening might be of help for high-risk wards (4). Moreover, an increasing number of studies indicated the importance of active surveillance for vancomycin-resistant enterococci (VRE) in the intestinal tract and for methicillin-resistant *Staphylococcus aureus* (MRSA) in the upper respiratory tract and skin in order to limit their spread (7-8).

Both cultural methods on selective plates and molecular systems directly from rectal swabs (for CRE, ESBL, CRAB, CRPA and VRE) or nasal/skin swabs (for CRAB, CRPA and MRSA) have been implemented in an increasing number of hospitals to detect MDRO and in most cases depend on the local epidemiology and on the internal hospital organization, in most cases without a standard guideline at national or international level.

Scope

In this manual, we suggest a standard operating procedure for patient selection and screening criteria with the application of possible diagnostic workflows for the detection of MDRO.

General principles/information and definitions

Definitions:

- **CRE:** carbapenem-resistant *Enterobacterales*
- **VRE:** vancomycin-resistant enterococci
- **ESBL:** extended spectrum beta-lactamase
- **MRSA:** methicillin-resistant *Staphylococcus aureus*
- **CRAB:** carbapenem-resistant *Acinetobacter baumannii*
- **CRPsA:** carbapenem-resistant *Pseudomonas aeruginosa*
- **MDRO:** multidrug resistant organism
- **NAAT:** nucleic acid amplification technology
- **LFIA:** lateral flow immunochromatographic assay

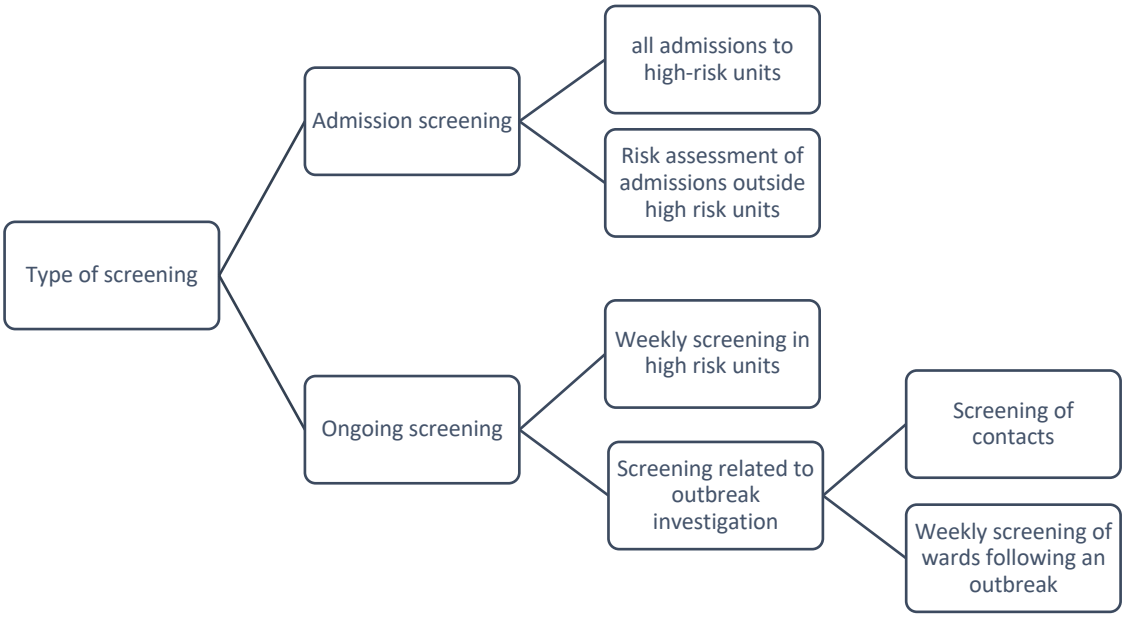
Procedures and steps

Active surveillance: who should be screened and when

The first step for the introduction of an active MDRO surveillance is the selection of eligible patients. Patients' selection criteria should present the following priority:

- High-risk patients such as patients admitted to hematology/oncology, transplantation, dialysis, and intensive care units, that present a higher probability to develop an infection by MDRO;
- As a second step, surgery and medical wards should be included in the screening up to the ideal inclusion of all hospitalized patients, including, if possible, also external elderly residency and rehabilitation units as final step.

Fig 13: Screening flow



Patients included in the screening should be subjected to the first control on admission, in order to implement adequate isolation and prophylaxis measures and minimize the possibilities of MDRO pathogens spread to other patients. Patients with risk factors should be considered to be preemptively isolated and on contact precautions pending the microbiological results.

Intestinal colonization by CRE (strong evidence) or VRE (low evidence) should be carried out with rectal swabs, while MRSA are usually screened on upper respiratory tract and/or skin swabs (for example for prophylaxis before cardiac surgery).

As above mentioned, reporting the screening of CRAB and CRPsA (moderate evidence) from rectal swabs can be a useful information, even if their absence is not sufficient to exclude the possible colonization in other -sites(for example skin or upper respiratory airways).

Active surveillance on ESBL is actually not recommended by most guidelines (very low evidence) and could be complicated in settings presenting a high endemicity level (higher than CRE, which should be prioritized). However, the implementation of ESBL screening in specific high-risk wards might be advisable.

What to do with patients negative for MDRO at admission

Patients admitted to high risk unit negative on admission should be subjected to serial screening (ideally once a week) during hospitalization to exclude the possibility of intra-ward transmission.

What to do with patients positive for MDRO at admission

Patients tested positive for MDROs on admission should be serially screened (ideally once a week) to detect the possible emergence of colonization by other MDROs (different species/mechanism of resistance).

MDRO cultural screening

Different cultural methods can be applied including for example direct plating on selective plates for Gram-negative pathogens (for example MacConkey agar) plus a carbapenem-disk (ertapenem or meropenem), or CNA agar with a vancomycin disk for VRE or Mannitol Salt agar plus cefoxitin disk for MRSA but the use of chromogenic selective plates is actually recommended (different commercial plates are available for CRE, ESBL, VRE and MRSA) due to the easier reading of the different morphologies basted on different pigmentations. Regarding CRE screening, the use of specific chromogenic commercial biplates (for example ChromID CARBA/SMART agar from bioMèrieux) which also present a high sensitivity for the detection of OXA-48 carbapenemases, is advisable.

CRPA and CRAB, might be isolated in most chromogenic selective plates for CRE, but some commercial plates have also recently become available for *A. baumannii* (es. CHROMagar™ *Acinetobacter*).

The use of a growth control plate (for example blood agar) is recommended in order to confirm sample eligibility.

After bacterial growth, both species and resistance mechanism identification should be carried out for several purposes including strain storage for possible outbreak characterization or antimicrobial susceptibility testing.

Species identification should be carried out by MALDI-ToF mass spectrometry or, alternatively (if the technology is not yet available), biochemical methods.

Characterization of the resistance mechanism on isolated colonies

Resistance mechanism identification from isolated colonies can be carried out by several methods, including molecular detection by end-point or Real Time PCR (either home-made or commercial methods) or LFIA.

The most common carbapenemase types are KPC, NDM, VIM, OXA-48 and IMP (9), which are generally covered by most commercial RT-PCR or LFIA methods, but less common allelic variants or other rarer carbapenemase genes might be undetected and the use of a carbapenemase-hydrolysis detection method (carba-NP, carbapenem-inactivation method or spectrophotometric β-lactamase activity

assays) might be advisable in case of growth on selective plates but negativity to most common carbapenemase genes (and the isolates should be subjected to further characterization by WGS in case of positivity).

Regarding MRSA, the most common resistance gene is *mecA,* but the use of methods able to detect also the less common *mecC* gene is advisable (10).

The most common VRE are represented by VanA-producing *Enterococcus faecium*, but less commonly also VanA-producing *Enterococcus faecalis* or VanB-producing *E. faecium* or *E. faecalis* can be found (11). *Enterococcus casseliflavus* and *Enterococcus gallinarum*, which present an intrinsic low-level vancomycin-resistance phenotype due to the production of a chromosomally encoded VanC operon, should not be considered as relevant for infection control purposes due to their limited clinical significance.

MDRO direct molecular screening

Direct detection of resistance mechanisms by molecular methods can be more expensive and require additional instruments and personnel expertise, but significantly reduces time to result (from 24-48 hours of cultural methods coupled with resistance mechanism identification to 1-5 hours of direct molecular methods) (Figure 13).

Different commercial methods are available nowadays for the detection of the most common carbapenemases, *vanA/B* and *mecA/C* genes (in the latter case coupled with probes for *Staphylococcus aureus* identification and the junction between the SCC*mec* element and *S. aureus* chromosome to discriminate from methicillin-resistant coagulase-negative pathogens).

The most important carbapenemase types (see previous paragraph) should be covered (for CPE), possibly including the highest number of possible allelic variants (considering the local epidemiology).

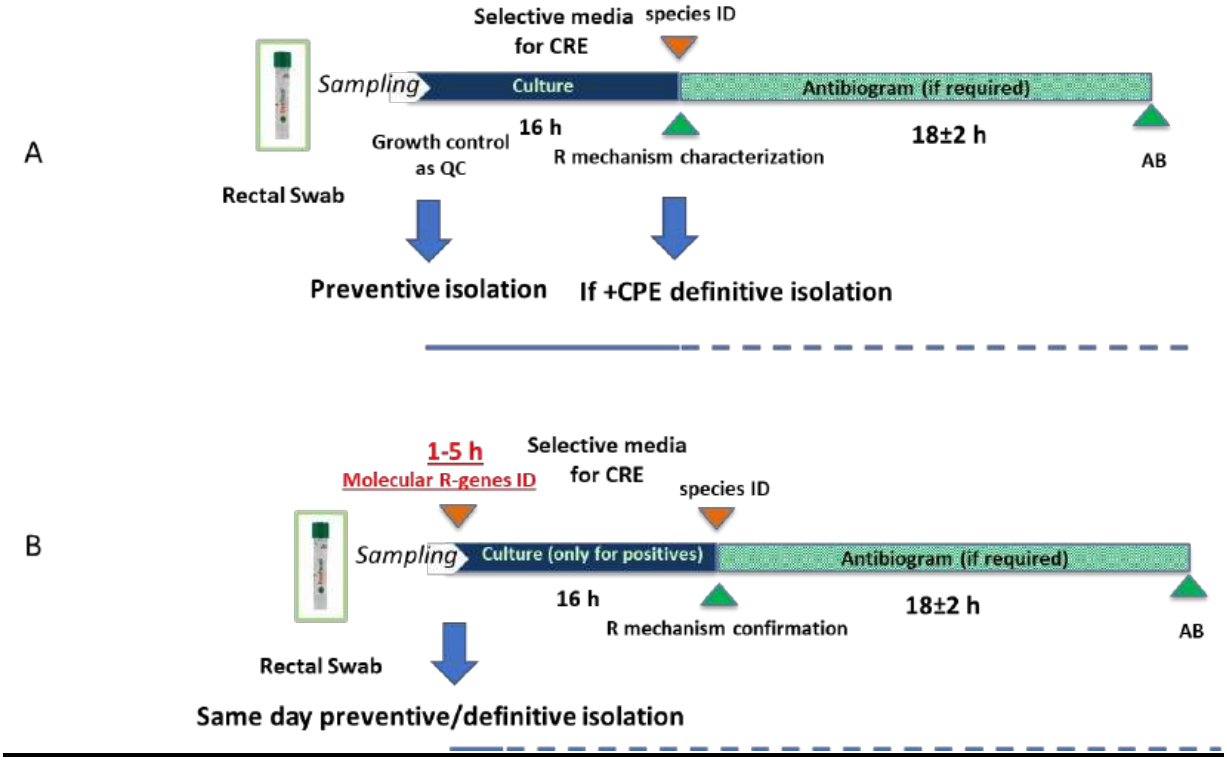
Direct detection of VRE from rectal swabs should be restricted to *vanA* gene, since *vanB*-carriers might be present in the anaerobic intestinal flora (12-13).

Resistance gene detection can be sufficient for patient isolation but should be coupled by culture of molecular positive samples for species identification. Cultural methods following molecular positivity can also allow antimicrobial susceptibility testing, which can be useful in some cases (14).

The result of direct molecular testing can be important to limit preventive isolation measures for patients upon admission compared to cultural methods, potentially reducing the overall costs for the healthcare system, counterbalancing the additional costs in terms of instruments, reagents, and personnel for the microbiology laboratory (14).

Finally, the setup of a preliminary reporting system able to communicate MDRO screening results to clinicians is crucial for the rapid implementation of isolation measures (or de-implementation in case of negativity).

Figure 14. Schematic representation of the different workflows of CRE screening by cultural methods (A) and direct molecular methods from rectal swabs (B).



Requirements:

- Selective plates for MDRO screening.
- Identification method by mass spectrometry (MALDI-ToF) or biochemical ID.
- Dedicated instruments and trained personnel for DNA extraction, amplification and results interpretation.
- Training of microbiologist and healthcare workers (HCW) to ensure good understanding of MDROs and their role in the management of colonized patients.

Material and Resources & Responsibilities

Human resources:

Actors	**Roles**
Laboratory Technicians of the Microbiology unit	Appropriate formation on sample management and extraction and amplification procedures
Microbiologist	Screening results interpretation, communication, and reporting
Clinicians	Rapid acknowledgement of colonization status

Indicators

Indicators to track implementation and progress

Process indicators:

- Number of patients screened upon 1000 admission/ year
  Stratify by CRE/CRPA/CRAB
- MDRO positivity percentage/ year
  Stratify by CRE/CRPA/CRAB

References:

[1] van Duin D, Paterson DL. Multidrug-Resistant Bacteria in the Community. Infect Dis Clin North Am 2016;30:377–90. doi:10.1016/j.idc.2016.02.004.

[2] Bartal C, Rolston KVI, Nesher L. Carbapenem-resistant *Acinetobacter baumannii*: Colonization, Infection and Current Treatment Options. Infect Dis Ther 2022;11:683–94. doi:10.1007/s40121-022-00597-w.

[3] Paulsson M, Su Y-C, Ringwood T, Uddén F, Riesbeck K. *Pseudomonas aeruginosa* uses multiple receptors for adherence to laminin during infection of the respiratory tract and skin wounds. Sci Rep 2019;9:18168. doi:10.1038/s41598-019-54622-z.

[4] Tacconelli E, Cataldo MA, Dancer SJ, De Angelis G, Falcone M, Frank U, *et al*. ESCMID guidelines for the management of the infection control measures to reduce transmission of multidrug-resistant Gram-negative bacteria in hospitalized patients. Clin Microbiol Infect 2014;20:1–55. doi:10.1111/1469-0691.12427.

[5] European Centre for Disease Prevention and Control. Carbapenem-resistant *Acinetobacter baumannii* in healthcare settings-8 December 2016. Stockholm: ECDC; 2016; https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/8-Dec-2016-RRA-Acinetobacter%20baumannii-Europe.pdf.

[6] Guidelines for the Prevention and Control of Carbapenem-Resistant *Enterobacteriaceae*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* in Health Care Facilities. Geneva: World Health Organization; 2017. Available from: https://www.ncbi.nlm.nih.gov/books/NBK493061/

[7] Calfee DP. Methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci, and other Gram-positives in healthcare. Curr Opin Infect Dis 2012;25:385–94. doi:10.1097/QCO.0b013e3283553441.

[8] Price CS, Paule S, Noskin GA, Peterson LR. Active Surveillance Reduces the Incidence of Vancomycin-Resistant Enterococcal Bacteremia. Clin Infect Dis 2003;37:921–8. doi:10.1086/377733.

[9] Hansen GT. Continuous Evolution: Perspective on the Epidemiology of Carbapenemase Resistance Among *Enterobacterales* and Other Gram-Negative Bacteria. Infect Dis Ther 2021;10:75–92. doi:10.1007/s40121-020-00395-2.

[10] Paterson GK, Harrison EM, Holmes MA. The emergence of *mecC* methicillin-resistant *Staphylococcus aureus*. Trends Microbiol 2014;22:42–7. doi:10.1016/j.tim.2013.11.003.

[11] Selim S. Mechanisms of gram-positive vancomycin resistance (Review). Biomed Reports 2021;16:7. doi:10.3892/br.2021.1490.

[12] Stinear TP, Olden DC, Johnson PD, Davies JK, Grayson ML. Enterococcal *vanB* resistance locus in anaerobic bacteria in human faeces. Lancet 2001;357:855–6. doi:10.1016/S0140-6736(00)04206-9.

[13] Ballard SA, Pertile KK, Lim M, Johnson PDR, Grayson ML. Molecular Characterization of *vanB* Elements in Naturally Occurring Gut Anaerobes. Antimicrob Agents Chemother 2005;49:1688–94. doi:10.1128/AAC.49.5.1688-1694.2005.

[14] Ambretti S, Bassetti M, Clerici P, Petrosillo N, Tumietto F, Viale P, *et al*. Screening for carriage of carbapenem-resistant *Enterobacteriaceae* in settings of high endemicity: a position paper from an Italian working group on CRE infections. Antimicrob Resist Infect Control 2019;8:136. doi:10.1186/s13756-019-0591-6.

Outbreak Management

Title	Outbreak investigation
Document status	Approved by on
Version Number	
Authors	A.Nguyen, S.Harbarth

Introduction

MDROs (Multidrug Resistant Organisms) outbreaks have the potential to cause widespread disruption to clinical services, limit the ability to perform medical procedures, cause harm and emotional stress to individual patients, and have widespread financial costs, logistical and reputational consequences. Outbreaks of MDROs happen mainly following silent transmission from patients whose colonisation are not recognised or swiftly contained. It is essential that MDROs detection is appropriately managed to prevent onward transmission.
Multiple outbreak approaches have been described and published, showing a variability/heterogeneity of management strategies implemented to tackle the situation. To investigate and control such incident requires a robust IPC (Infection Prevention and Control) approach with a reactive multidisciplinary team able to assess the risk, coordinate the response with a clear action plan, communication and strong collaboration. Steps to control outbreaks are not complicated but implementation, coordination and strict compliance is complex, although necessary, as these organisms are unforgiving.

Scope

This document provides guidance and support to all the participating hospitals included in REVERSE, to manage an outbreak of MDROs, such as CRE (carbapenem-resistant Enterobacterales (CRE), CRPsA (carbapenem-resistant *Pseudomonas aeruginosa)* and CRAB (carbapenem-resistant *Acinetobacter baumannii)*. This is only a guidance, offering some tools and a pragmatic approach but cannot answer all the different types of situations. Its aim is not to replace or overcome a local outbreak management procedure but just to offer a support. The local team has to self-assess the outbreak and define which tool might be the more useful and available in the context, depending of the local epidemiology, the available resources and the technical capacities.

General principles/information and definitions

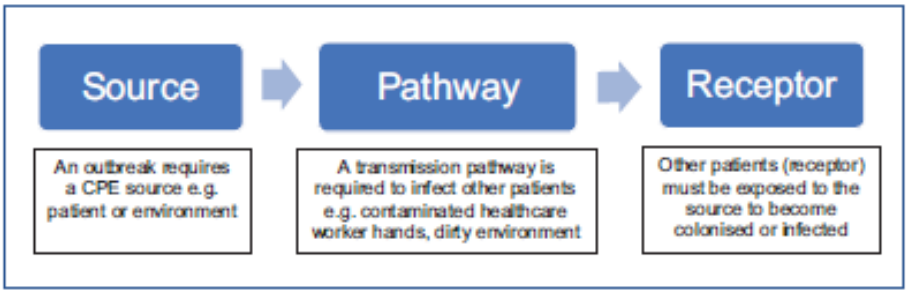
Definitions:

- **Case definition:** criteria specific to the outbreak under investigation, comprising a specific MDROs strains or resistance mechanism, within a defined timeline, and a specific geographic area
- **Contact case:** any patient having shared the same clinical space or being taken in charge by the same medical/nurse team, day or night
- **Index patient:** the first documented patient in an epidemic situation
- **Outbreak:** A state characterised by an increased incidence of cases greater than what is typically expected in a particular healthcare setting (over expected rates). Cases clustered temporally or geographically or by microorganism or mechanism of resistance, suggest that the cases are from a common source or secondary to increased person-to-person transmission.

A single case for example of a new carbapenem resistant mechanism may indicate an unrecognized outbreak.

Fundamentals of outbreak control:

- "Tip of the iceberg": the detection of MDROs in a clinical sample suggest strongly an undetected carriage and a potential transmission, as the ratio between colonisation and infection is usually high.
- "Ring screening": the detection of MDROs case should trigger the screening of all contact patients in concentric circles around the index patient
- "Every minute counts": the rapid detection and isolation of MRDO index cases and their contacts is critical.
- Transmission pathway: separation of one of the three components (source, pathway or receptor) can lead to breaking the chain of transmission and so the outbreak.
  Figure 15 reproduced from Puleston et al.: transmission pathway



- "Walking forward": staff should start their work/ward visit from "clean" (uncolonized) patients finishing with the MDROs patients.

Procedures and steps

Requirements:

- Effective leadership by senior management
- Outbreak control team (multidisciplinary team):
  - Ensure the team comprises individuals with experience of outbreak management (IPC or infectious diseases specialist, clinical microbiologist, staff of the concerned ward)
  - Regular meetings with robust planning skill to develop a clear action plan
  - Clear distribution of roles and responsibilities
- **Local MDRO outbreak management plan** for responding to a general increase in cases, a local cluster or wider outbreak
- Rapid reminder (posters, leaflet, training) for strict adherence to MDROs management and standard IPC procedures
- Education of healthcare workers (HCW) to ensure good understanding of MDROs and their role in the management of the outbreak.

Managing an outbreak:

1. **Detect and Recognise the outbreak**

   One new clinical case of MDRO infection can already be considered as the first sign of an ongoing silent transmission and requires triggering an investigation.
   Therefore, it is important to:

- Review **regularly** the current epidemiology data in the hospital for example during IPC meetings, incident meetings or laboratory meetings (draw epidemic curve).

- Optimise the laboratory system (methods and surveillance data) to be able to identify rapidly colonised or infected cases and monitor confirmed cases with clear pathways of communication. Automated alerts based on laboratory data should be a key part of such systems to ensure deviations from the norm can be identified e.g. observed increase in proportion of CPE screens that are positive.
- Ensure good communication of the outbreak, both internally (ward staff, management team…) and externally including notification to patient and relatives.
- Communicate to REVERSE team (as described by the "REVERSE outbreak characterization" protocol " and discuss the request for sequencing of the different strains in selected outbreaks).

2. <u>Management of the newly infected or colonised cases & contacts</u>

A. Flag (Alert) each new patient colonised or infected

- Inform and communicate adequately to patient and staff (management, ward, laboratory, cleaning services).
- Produce and update regularly an outbreak curve.

B. Adopt a screening strategy appropriate to the situation, with the aim of identifying potential cases (exposed contacts)

The definition of a MDRO contact will depend on several factors, including:

- The setting: proximity with the index case, high risk area (ICU, haemato-oncology, transplant unit, hemodialysis), contact precautions or standard precautions in place ahead
- Clinical scenario: type of patient, dependency level requesting care by HCW, clinical symptomatology (diarrhea, draining wounds…)
- Type and length of exposure (delay in identification and isolation of cases)

It is essential to develop a dynamic registry of cases and contacts allowing identifying the epidemiological links such as mapping patient movement and analyzing patient networks (leading to identify and remediate an environmental reservoir).
MDROs contacts are most commonly defined as having shared the same clinical space (e.g. room, bay or less commonly ward) as a (un/)known MDROs carrier for 24 hours. Contacts of patients newly identified as MDROs positive need to be screened to detect possible transmission as further carriers may be detected. The number of contacts to be screened will be determined by the hospital IPC team on a case-by-case basis based on proximity to the index case, duration of exposure, and shared staff. In high-risk units, hospitals should strongly consider broader screening for example all patients on these wards.
When MDRO-positive patients are found among screened contacts, the strategy for further screening of patients needs to be expanded. An enhanced period of screening should be conducted especially during the outbreak period.
As an example, patients in the affected unit/bay/ward should be screened once or twice a week for two weeks, and weekly for a further two weeks. Once no new cases are detected, the frequency of screening may be reduced and stopped at an appropriate point in time after no further cases have been detected. While there is no evidence to suggest how long this process should take, we suggest a pragmatic period of between 2 and 8 weeks.
Screening of patients already discharged from an outbreak ward to their usual home setting is not generally recommended. However, flagging of households can alert patients requiring screening on (re-)admission to hospital.
Information on the patient's potential exposure to MDROs should be included on any inter-hospital or intra-hospital transfer documents and/or discharge summary to alert relevant healthcare providers (including general practitioners).

It is important to:

- Consider to isolate pre-emptively a contact patient who shared the same room of a MDRO patient (before the instauration of additional precautions) or in case the patient stayed in the same unit with the same staff in charge when there is a secondary MDRO case.
- Consider active surveillance of a ward following an outbreak for example with screening once weekly or/and on admission particularly in high-risk units such as ICU, graft ward, haemato-oncology…

For screening, the body sites to be sampled depend on the organism. CPE most commonly require samples of stool or rectal swab (See manual for active surveillance)

C. Isolation approaches to develop for single cases or larger outbreak

- Isolate in a single room with en suite bathroom/facilities (or dedicated commode if no en suite)
  Or
- Group patients within a dedicated area (cohorting patients), when the mechanism of carbapenem resistance is the same, especially when there is limitation in term of single rooms available.
- Ensure dedicated equipment or single-use items for MDROs colonised or infected patients; where equipment must be reused, ensure appropriate disinfection;
- Reusable non-invasive care equipment should be dedicated to the isolation room/cohort area and decontaminated prior to use on another patient.
- Organise new admissions to avoid contact with the others sectors (such as MDROs cases and contact patients); consider to stop admission in the unit until reorganisation (closing wards) weighing carefully the risk of decreased access to care.
- Define approaches to internal/external patients transfer to minimize the risk of infection transmission;
- Inform the others units/department if contact patient transferred; communication needs to occur prior to the affected patient's transfer or discharge.

D. Urgent/Prompt control measures: Reinforce the standard IPC practices & audit and feedbacks

- Optimize IPC practices ensuring a high level of strict applications of standard precautions (hand hygiene,…) to limit transmission and audit them; (highlight the existing deficiencies)
- Instore additional contact precautions for MDROs carriers or infected patients; the additional precautions especially for contact patient should not prohibit the patient to receive the care needed.
- Environment: reinforce cleaning/disinfection approaches especially for MDRO carriers or infected patients (disinfection, enhancing frequency); underline cleaning of high-touch surfaces or equipment; increase the frequency of cleaning toilets in outbreak wards.
- Enhance the process of terminal cleaning when the patient leaves.
- Organise care "from clean to dirty" or"Walking forward": known colonised or infected patients should be put at the end of the list of work without compromising the patient management.
- Monitor antibiotic selection pressure through antibiotic stewardship programmes: review antimicrobial prescribing practices.

3. Staffing

- Determine and implement staffing requirements to manage an outbreak situation (optimise staff-to-patient ratios)
- Try to have dedicated staff (staff cohorting) to the area with MDRO carriers or infected patients
- Minimise transfer of staff from affected unit to unaffected unit
- Offer education & training

4. Investigation of the potential source

A. Look for the source of the outbreak either secondary to increased person-to-person transmission (from colonised patient) or from a common source (environment).
- Consider if the acquisition could have been before the admission, meeting criteria for a suspected case on admission, for example having a history of inpatient in another hospital.
- Undertake epidemiological assessment in an attempt to identify the source (root cause analysis) and/or assess the effectiveness of interventions.
- Develop hypotheses.
- Describe patients' trajectory in the hospital-review patient healthcare exposures prior and after the initial positive culture.
- Screen contact patients in contact with the index patient before the initial diagnosis.
- Interview staff.
- Review procedure searching potential exposure risk such as shared patient equipment, rooms, surgical interventions or procedures.
- Investigate environmental reservoirs if this is indicated or appropriate, for exemple for organism with a known persistence in the environment (e.g, Acinetobacter spp). There is some evidence that MDRO may contaminate sinks, shower waste traps, toilets which then can transmit to patients.
- Consider whole genome sequencing to understand the chain of transmission (see specific REVERSE procedure).
- Environmental sampling: its role is controversial for the management of outbreak; it needs discussion among the outbreak team, guidance from microbiology with suitable sites and sampling method to be determined.

5. End of an outbreak

There is no clear consensus on when to define the end of an outbreak. An outbreak can be considered controlled when 2-3 series of samples are negative among the contacts or the unit, after 2-4 weeks since the first case.
It is important after the control of the outbreak that:
- IPC team writes a report analysing the factors contributing to the outbreak, the actions done and provides recommendations in the short or long term to prevent such outbreak, minimise the spread of MDROs.
- Flag the patient discharged: this could allow them to be screened when they are readmitted and put pre-emptively in isolation.
- Check the preparedness by updating the outbreak/clusters management plan

Material and Resources & Responsibilities

Human resources:

Actors	**Roles**
Staff of the unit	IPC measures in place: strict adherence to standard and additional precautions
IPC team- *Key coordinator*	Inform the team, control the application of the IPC measures adequately in the unit Tracking patients and contacts Investigate the outbreak Communication Reporting
Cleaning team	Strict adherence to cleaning standards

Laboratory microbiology	Identify potential cases: rapid identification of acquired carbapenemases and rapid communication to the clinical team
Administration /informatics	Flagging Epidemiologic curve surveillance
REVERSE WP3 (IPC team)	Support to local IPC team

Indicators

Indicators to track implementation and progress

Process indicators: None
Reporting:

- Number of outbreaks during the IPC and ABS intervention in the REVERSE wards: Reporting every 6 months: location (wards, units) /number of patients involved/ pathogens/main actions
- Number of outbreaks support with strains characterization by UNIFI laboratory (See protocol for sending sample to UNIFI)



REVERSE outbreak characterization.docx

Appendices

Tools:

- Appendix 1 :Basic Outbreak checklist
- Appendix 2: Case contact spreadsheet
- Appendix 3: Information flyer for patient



Patient leaflet.docx

References:

1. Scotland ARHAI NHS. Literature Review: healthcare infection incidents and outbreaks in Scotland. 2022.

2. Beck-Sague C, Jarvis WR, Martone WJ. Outbreak investigations. Infect Control Hosp Epidemiol. 1997;18(2):138-45.

3. Puleston R, Brown CS, Patel B, Fry C, Singleton S, Robotham JV, et al. Recommendations for detection and rapid management of carbapenemase-producing Enterobacterales outbreaks. Infect Prev Pract. 2020;2(3):100086.

4. Poulou A, Voulgari E, Vrioni G, Xidopoulos G, Pliagkos A, Chatzipantazi V, et al. Imported Klebsiella pneumoniae carbapenemase-producing K. pneumoniae clones in a Greek hospital: impact of infection control measures for restraining their dissemination. J Clin Microbiol. 2012;50(8):2618-23.

5. Frattari A, Savini V, Polilli E, Di Marco G, Lucisano G, Corridoni S, et al. Control of Gram-negative multi-drug resistant microorganisms in an Italian ICU: Rapid decline as a result of a multifaceted intervention, including conservative use of antibiotics. Int J Infect Dis. 2019;84:153-62.

6. Rodriguez-Bano J, Garcia L, Ramirez E, Martinez-Martinez L, Muniain MA, Fernandez-Cuenca F, et al. Long-term control of hospital-wide, endemic multidrug-resistant Acinetobacter baumannii through a comprehensive "bundle" approach. Am J Infect Control. 2009;37(9):715-22.

7. Meschiari M, Lopez-Lozano JM, Di Pilato V, Gimenez-Esparza C, Vecchi E, Bacca E, et al. A five-component infection control bundle to permanently eliminate a carbapenem-resistant Acinetobacter baumannii spreading in an intensive care unit. Antimicrob Resist Infect Control. 2021;10(1):123.

8. Swissnoso. Gestion des épidémies dues à des bactéries multirésistantes (BMR). 2022.

Appendix 1 : Basic Outbreak Checklist

- ☐ Outbreak team
- ☐ Action plan for ongoing investigations and control measures
- ☐ Index patient (s)
  - ☐ Additional precautions in place
  - ☐ Isolation or cohorting
  - ☐ Flag/Alert
  - ☐ Line list of cases (epidemic curve)

- ☐ Reinforce promptly infection prevention and control measures
  - ☐ Standard precautions
  - ☐ Contact precautions
  - ☐ Education & awareness to ward staff
  - ☐ Audit & feedbacks

- ☐ Identify contact patients
  - ☐ Screening (schedule& list of case-contacts)
  - ☐ Pre-emptive isolation
  - ☐ Additional precautions
  - ☐ Flag contact patients
  - ☐ If positive detection
    - ☐ Isolation
    - ☐ Additional precautions
    - ☐ Cohorting (depending of patients number)
    - ☐ Staff cohorting

- ☐ Information & communication
  - ☐ Hospital direction/management
  - ☐ Ward staff
  - ☐ Health environmental hygiene team
  - ☐ Laboratory
  - ☐ Authorities (depending of each local/regional/national requirements & laws)
  - ☐ Patient & relatives

- ☐ Health environmental hygiene
  - ☐ Reinforce cleaning (product, schedule…)
  - ☐ Improve cleaning of high touched surfaces

- ☐ Audit & feedbacks

- ☐ Investigate the source
  - ☐ Contact- case with community acquisition-- silent transmission
    - ☐ Strains sequencing
  - ☐ Equipment shared
  - ☐ Procedures/interventions
  - ☐ Environmental reservoir (aquatic for ex.)
    - ☐ Environmental sampling

Appendix 2: Case-contact spreadsheet (template for local adaptation)

Date first case identified: __ /__ /____ Sample:	Contact details: Date of birth: Sex:	Ward: Room:
Count of cases colonised or infected by_____ as of: __ /__ /____ (insert date) Number of case-contacts screened: Number of case-contacts positive with same strain:		

Case-contact Name	Admission	Screening	Result (laboratory)	Measures implemented	Contact of the case-contact
	Date: __ /__ /____ Ward/Room:	N°__ Date: N°__ Date: N°__ Date:	☐ Positive ☐ Negative ☐ unknown	*Flag* *Contact precautions* *Isolation…*	
	Date: __ /__ /____ Ward/Room:	N°__ Date: N°__ Date: N°__ Date	☐ Positive ☐ Negative ☐ unknown		
	Date: __ /__ /____ Ward/Room:	N°__ Date: N°__ Date: N°__ Date:	☐ Positive ☐ Negative ☐ unknown		
	Date: __ /__ /____ Ward/Room:	N°__ Date: N°__ Date: N°__ Date:	☐ Positive ☐ Negative ☐ unknown		
	Date: __ /__ /____ Ward/Room:	N°__ Date: N°__ Date: N°__ Date:	☐ Positive ☐ Negative ☐ unknown		

Molecular analysis and sequencing of isolates for outbreak investigation

Title	Molecular analysis and sequencing of isolates for outbreak investigation
Document status	Approved by On
Version Number	1
Authors	Marco Coppi, Alberto Antonelli, Chiara Bonaiuto, Ilaria Baccani, Tommaso Giani, Gian Maria Rossolini

Introduction

The constant increase of multidrug-resistant organisms (MDRO) is threatening health-care systems around the world.
World Health Organization (WHO) enumerated a list of 12 species against which the discovery of new antibiotics is urgently required, including multidrug-resistant *Mycobacterium tuberculosis*, carbapenem-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, carbapenem-resistant and/or 3rd generation cephalosporin-resistant *Enterobacterales*, vancomycin-resistant *Enterococcus faecium* and methicillin- vancomycin-resistant *Staphylococcus aureus*. (Tacconelli *et al*, 2018). Among *Enterobacterales*, *Klebsiella pneumoniae* isolated from invasive infections reached in Europe high resistance rates for third-generation cephalosporins (33.9%), followed by fluoroquinolones (33.8%), aminoglycosides (23.7%) and carbapenems (10.0%), with remarkable geographic variability (ECDC, 2022). High level of broad-spectrum antibiotics usage, inadequate hand hygiene, exposure to infections in hospitals, patient comorbidities and use of medical devices are known risk factors for colonization or infection with MDRO. (Mulani, 2019; Thoma, 2019).
Genotyping MDRO strains is important to understand the complexity and multifaceted nature of MDRO transmission in hospitals and to evaluate the efficacy of Infection Prevention and Control (IPC) measures in healthcare settings. In this perspective, studying hospital outbreaks by using molecular assays combined with clinical and epidemiological data, is crucial in order to identify index case, infer transmission dynamics, appropriately allocate prevention resources and implement control measures.
The current gold standard for the analysis of MDRO outbreak isolates is represented by whole-genome sequencing (WGS), followed by integration of data analysis with clinical and epidemiological information, which represents the most crucial part of the analysis requiring high level of expertise.
Nevertheless, microbiology laboratories able to include WGS analysis of local outbreak in their ordinary workflow are still limited as a result of logistical issues (costs and/or expertise). Therefore, traditional PCR-based approaches (e. g. repetitive element palindromic (REP) PCR or random amplification of polymorphic DNA (RAPD)) combined with multilocus sequence typing (MLST) are still used (Nutman, 2018).

Scope

This document provides information to the focal points in the outbreak investigation workflow using molecular and WGS approaches. All the participating hospitals included in REVERSE project will be given the technical support needed to characterize a local outbreak with genotypic analysis. During

REVERSE project a sequencing and analysis service will be provided using the molecular approaches and tools reported in this document.

General principles/information and definitions

Definitions:

- **LFIA**: lateral flow immunochromatography assay, is a rapid and cheap method to detect resistance gene's antigens.
- **WGS:** whole genome sequencing is a molecular approach which allows bacterial genome characterization.
- **AST**: antimicrobial susceptibility testing
- **MLST:** Multi locus sequence typing is a molecular method for the characterization of strain's clonality based on the analysis of the allelic variant of 6-7 housekeeping genes.
- **Outbreak**: represents a particular condition characterized by an increased level of infection or colonization cases in a restricted healthcare setting (i.e. ward). Infections' onset should cluster temporally and geographically and should share the same microorganism and/or resistance mechanism, suggesting the possibility of a common initial source followed by cross-transmission within the healthcare setting.

Procedures and steps

Requirements:

- Molecular biology team:
  - Laboratory technicians with molecular biology expertise
  - Microbiologist with bioinformatics expertise
- LFIA or genotypic methods for resistance mechanism characterization
- DNA extractors
- Library preparation reagents
- Next Generation sequencing platforms
- Dedicated raw data storage and software for data analysis
- Metadata obtained thanks to Outbreak Management SOP

Managing outbreak molecular analysis:

6. Sample selection and storage

Each hospital belonging to the REVERSE project, once identified an MDRO outbreak (see outbreak definition above and SOP on outbreak management) should start the molecular analysis by collecting putatively involved isolates.

Species identification (ID), antimicrobial susceptibility testing and characterization of the resistance determinants should be performed following their standard protocols:

- matrix-assisted laser desorption ionization–time of flight mass spectrometry or biochemical profiling for species ID;
- reference broth microdilution method or automated systems for AST;
- molecular testing on isolated colonies such as PCR- or array-based platforms or LFIA for resistance determinant characterization.

All isolates should be stored at -80°C in Brain Heart Infusion broth (BHI) containing 20% v/v glycerol or other dedicated cryovials and used for further characterization.

Note: From this point, the laboratory in collaboration with the infection prevention and control team can decide to either send the strains to the University of Florence (UNIFI, reference laboratory for outbreak investigation within REVERSE project) for subsequent WGS and

bioinformatics analysis or to follow the passages reported below to further characterize outbreak strains.

7. DNA Extraction methods

After bacterial growth on agar plates (for example blood agar or chromogenic plates or selective plates for MDRO), where colony morphology will be investigated in order to check isolate purity, genomic DNA can be extracted using either automated or manual extraction kits (e. g. Qiagen DNeasy PowerLyzer PowerSoil Kit) following manufacturer's instructions. Before proceeding with whole genome sequencing, DNA should be quantified using either fluorimetric or spectrophotometric technologies (e. g. Qubit or NanoDrop, Thermo Fisher Scientific).

8. Whole Genome Sequencing

Samples DNA will be then diluted depending on genome concentration and DNA amount required by the selected sequencing platform. Libraries will be prepared following instructions provided by the Company of the selected WGS technology. Whole genome sequencing might be performed using different approaches and technologies, for instance: Illumina Miseq™/Nextseq™/Novaseq™ platforms (Illumina, Inc., San Diego, USA), Ion Torrent™ (Thermo Fisher Scientific Waltham, USA) technology or long reads platforms such as PacBio SMRT (CD Genomics, New York, USA) or Nanopore system (Oxford Nanopore Technologies, Oxford, UK) to obtain complete plasmid sequences. Moreover, external sequencing services might also be evaluated to limit personnel workload and instruments' costs (at costs in most cases <150 euro/sample). Sequencing services require quantified extracted DNA and produce raw genome information that should be subsequently analysed by the laboratory.

9. Bioinformatic analysis

Raw reads will be assembled using specific bioinformatic platforms such as SPAdes, available on KBase environment (Arkin, 2018). Multilocus sequence typing (MLST), species identification, porin status, antimicrobial resistance and virulence genes and phylogenetic analysis should be evaluated by using specific online tools which may also be open access. Few examples of open access and user-friendly platforms available online are be reported below:

Type of analysis	Tool name	Website
Species Identification, porin status, antimicrobial resistance and virulence genes, MLST, Phylogenetic analysis	ResFinder	http://genomicepidemiology.org/
	VFDB	http://www.mgc.ac.cn/VFs/
	Kleborate	https://pathogen.watch/
	MLST	https://cge.food.dtu.dk/services/MLST/
	Pathogen Watch	https://pathogen.watch/
	CSI phylogeny	https://cge.food.dtu.dk/services/CSIPhylogeny/
	ABRicate	
	Gubbins	https://usegalaxy.org/
	Snippy	

10. Contacts

For support for outbreak characterization, strains selection, AST with reference methods, WGS and data analysis you can contact Dr. Marco Coppi (marco.coppi@unifi.it) and Dr. Alberto Antonelli (alberto.antonelli@unifi.it) from UNIFI team.

Material and Resources & Responsibilities

Human resources:

Actors	Roles
Laboratory technician	Sample storage, ID, AST, RT-PCR or LFIA, DNA extraction, library preparation, WGS set up
Microbiologist	Selection of suspected outbreak strains, Genome data analysis
Microbiologist and hospital epidemiologist	Integration of WGS data with clinical and epidemiological data
UNIFI Team	Support on outbreak strains selection, resistance mechanisms characterization, AST, WGS and bioinformatics analysis

Indicators

Indicators to track implementation and progress

Process indicators:

- Concordance data on species ID, AST, resistance mechanism characterization and WGS analysis (when performed) between results locally obtained and the ones produced in the reference laboratory in case of outbreaks onset during the REVERSE project time of study.

Annexes

Outbreak Strain Characterization Protocol

References:

1. Tacconelli E, Carrara E, Savoldi A, *et al.* WHO Pathogens Priority List Working Group. 2018. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. Lancet Infect Dis. 18(3):318-327.
2. European Centre for Disease Prevention and Control. Antimicrobial resistance in the EU/EEA (EARS-Net) - Annual Epidemiological Report 2020. Stockholm: ECDC; 2022
3. Mulani MS, Kamble EE, Kumkar SN, *et al*. 2019. Emerging Strategies to Combat ESKAPE pathogens in the era of antimicrobial resistance: A Review. Front Microbiol. 10:539.
4. Thoma R, Seneghini M, Seiffert SN, *et al*. 2022. The challenge of preventing and containing outbreaks of multidrug-resistant organisms and *Candida auris* during the coronavirus disease 2019 pandemic: report of a carbapenem-resistant *Acinetobacter baumannii* outbreak and a systematic review of the literature. Antimicrob Resist Infect Control.
5. Nutman A, Marchaim D. 2018. How to: molecular investigation of a hospital outbreak. Clinical Microbiology and Infection 25(2019) 688-695.https://reader.elsevier.com/reader/sd/pii/S1198743X18306396?token=29D6670272D96660ED0429142E14CA92D4A6B2B2643D7B580E943DD1CC11EFDB8FA7080EE46FA4A205946B2B70B0FFBA&originRegion=eu-west-1&originCreation=20220913172837
6. Arkin AP, Cottingham RW, Henry CS, Harris NL, Stevens RL, Maslov S, et al. KBase: The United States Department of Energy Systems Biology Knowledgebase. Nature Biotechnology. 2018;36: 566. doi: 10.1038/nbt.4163

Healthcare environmental hygiene (HEH)

Title	Healthcare environmental hygiene for prevention and control of CRE, CRAB, CRPsA transmission
Document status	Approved by on
Version Number	
Authors	Aude Nguyen, Stephan Harbarth

Introduction

Hospital environments can be contaminated by multi-drug resistant organisms (MDRO) and thereafter infect or colonize vulnerable patients. The environment can contribute to pathogen transmission either by direct contact with contaminated surfaces or equipment or indirectly through the hands of healthcare workers. Contamination by MDRO may be found on various surfaces (floor, bed frame, furniture, patients' clothes, bed sheets), predominantly on frequently touched surfaces for a long survival period. The risk of cross-transmission is amplified by heavy workload, understaffing, high bed occupancy rates, and rapid bed turnover.

Therefore, maintaining a clean environment and appropriately decontaminating all relevant equipment is an essential component of any multifaceted infection prevention and control strategy (1, 2). As reported by Peters et al. (3), interventions in environmental hygiene correlate with reduction of HAI (4). However, the direct benefit of environmental hygiene in healthcare institutions is difficult to determine, as enhanced cleaning and disinfection is often incorporated in a bundle in response to an outbreak or cluster of MDRO patients. Additionally, there is no standard method for measuring actual cleanliness of surfaces or the achievement of certain cleaning parameters (e.g., adequate contact time of disinfectant) or for defining the level of microbial contamination that correlates with good or poor environmental hygienic practices. Consequently, there is no universally agreed guidelines or practical recommendations for environmental cleaning, especially routine surface cleaning and disinfection for CRE, CRAB, CRPsA in hospitals, neither detailed practical protocols for the cleaning process (methods, frequency).

The current WHO guidelines (5) recommend that compliance with environmental cleaning protocols of the immediate surrounding area (that is, the "patient zone") of patients colonized or infected with CRE (Carbapenem Resistant *Enterobacteriaceae)*, CRAB (Carbapenem Resistant *Acinetobacter baumannii*) and CRPsA (Carbapenem Resistant *Pseudomonas aeruginosa)* should be ensured. Multiple guidelines, recognizing the lack of evidence, still recommend to enhance cleaning and monitoring practice especially during outbreaks.

Cleaning requires sufficiently trained staff, ongoing monitoring (e.g. measurement of bioburden), education, constant upgrading of practice, and two-way communication between those responsible for cleaning and those responsible for infection control.
Cleaning practices vary considerably, even within the same hospital and health district, and these rely heavily upon available resources and managerial support.

Scope

This policy document provides practical guidance on healthcare environmental hygiene (HEH) to all the participating hospitals in REVERSE in the perspective to reduce CRE, CRAB, and CRPsA transmission and related healthcare-associated infections. It is based on various national recommendations and available tools.(6-10)

This should not replace already pre-existing institutional HEH protocols, but serves as a support to improve practices.

Performing enhanced cleaning of the patient zone could imply different aspects such as a change of the product/cleaning agents, for example the use of disinfectants for high touch objects and high contamination risk surfaces, an improvement in the technique by providing audits and feedbacks, or an increase in the frequency of cleaning.

The objective of this document is in the perspective of MDRO control, to support the reinforcement of cleaning, focusing on cleaning of patient environment, especially surfaces and objects frequently touched by patients and health care workers:

- By offering:
  - Tools to evaluate HEH realised in each hospital: self-assessment questionnaire
  - Monitoring tools: auditing practices (compliance) and feedbacks
  - Support to improve practices: education & training for cleaners, reminders, development of environmental cleaning schedules

- By proposing: the creation of a multidisciplinary group with cleaning and IPC staff, as well as the wards staff concerned, focusing on the need for a collaborative approach.
  Different staff groups, both clinical and non-clinical, will be responsible for cleaning different elements within an area; they need to work together to meet the cleanliness standard for the whole area.

General principles and essential components

Definitions (7, 8, 10, 11**)**

Antiseptic: An agent that can kill microorganisms and is applied to living tissue and skin.

Cleaning: the removal of visible organic matter including dirt, debris, blood, and bodily fluids using either the physical action of wiping/scrubbing or the chemical action of a surfactant or detergent and water to wet, emulsify or reduce surface tension. Micro-organisms are removed rather than killed.
Cleaning is the necessary first step of any sterilization or disinfection process. Some disinfectants are readily deactivated by organic matter. (Cleaning is a form of decontamination that renders the environmental surface safe to handle or use by removing organic matter, salts, and visible soils, all of which interfere with microbial inactivation.)

Contact time: The time that a disinfectant must be in contact with a surface or device to ensure that appropriate disinfection has occurred. For most disinfectants, the surface should remain wet for the required contact time.

Contamination: The presence of an infectious substance on hands or on a surface such as clothes, gowns, gloves, bedding, toys, surgical instruments, patient care equipment, dressings or other inanimate objects.

Decontamination: A process that removes or destroys contamination and therefore prevents microorganisms reaching a susceptible site in sufficient quantities to cause infection. Cleaning, disinfection and sterilization are all decontamination processes. In the context of the environment or non-critical equipment (i.e. equipment or devices that are in contact with intact skin only), the term is usually refers to cleaning and disinfection, either using separate cleaning and disinfecting agent in a two-step process, or a '2 in 1' product that cleans and disinfects in one-step.

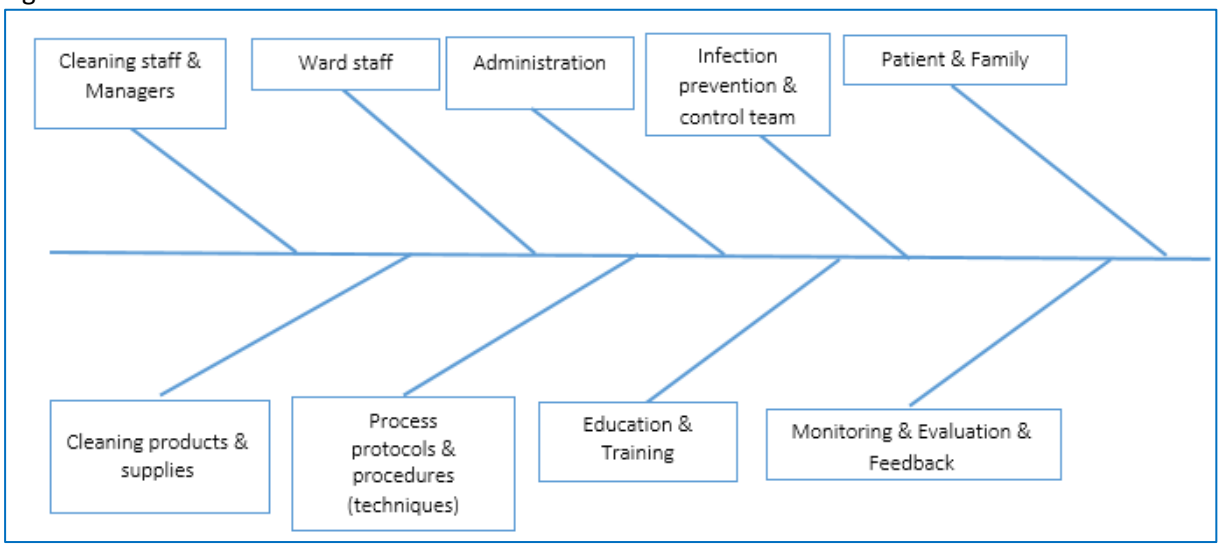
Detergent solution: synthetic cleansing agent that facilitates the removal of dirt and organic matter intended to be used in the cleaning of surfaces or other medical devices diluted with water as per manufacturer's instructions.
Discharge cleaning: cleaning of a room following transfer/discharge of a patient.
Disinfectant: chemical agent that rapidly kills or inactivates most infectious agents. Disinfection does not destroy bacterial spores.
Disinfection: Process of eliminating or reducing the number of viable microorganisms from inanimate objects and surfaces, by physical or chemical means. Disinfection should always be undertaken following, and in addition to, detergent cleaning.
Dual-purpose cleaner/disinfectant: a product that combines a detergent cleaning effect by surfactants and contains a biocide. Dual-purpose cleaner/disinfectants are designed to eliminate the need for separate cleaning and disinfection processes to be carried out consecutively by combining them into a single process.
Healthcare environmental hygiene (HEH) products: consumable products for cleaning or disinfection. Examples: cleaners and detergents or other chemical solutions
HEH supplies: tools for cleaning or disinfection. Examples: wipes, rags or sponges
High-touch surfaces: Surfaces and items, frequently touched by staff, patients and/or visitors requiring more frequent cleaning. High-touch surfaces are those that have frequent contact with hands. Examples include doorknobs, call bells, bedrails, light switches, wall areas around the toilet and edges of privacy curtains.
No touch modalities: automated process such as ultraviolet light devices and hydrogen peroxide vapor system
Patient zone: Immediate surroundings (space and objects) around a patient that may be touched by the patient and may also be touched by the health care provider when providing care; an area likely to be contaminated by the patient's bacteria.
In a multi-bed room, the client/patient/resident environment is the area inside the individual's curtain. Typically, this includes all inanimate surfaces that are touched by or in direct physical contact with the patient, such as the bed rails, bedside table, bed linen, infusion tubing, bedpans, urinals and other medical equipment. It also contains surfaces frequently touched by health care workers during patient care, such as monitors, knobs and buttons and other "high frequency" touch surfaces.
Sterilization: a process used to render an object free from microorganisms including viruses and bacterial spores.
Routine cleaning: Cleaning employed routinely to prevent the transmission of microorganisms that may cause HAIs.
Terminal cleaning: double cleaning of a room (routine cleaning and cleaning inaccessible surface) following transfer/discharge of a patient where transmission based precautions were required includes cleaning of some low frequency hand touch surfaces (emphasis on horizontal surfaces) and high frequency hand touch surfaces, that are not accessible when the room is occupied.
Terminal cleaning will reduce the risk that patients subsequently admitted to the same room will acquire pathogens from contaminated surfaces.

General principles

Health care settings should design their HEH structure to ensure accountability at all levels and should have:

a. Individuals with assigned responsibility for the cleaning of the physical facility.
b. Supervisors with responsibility for ensuring adherence to occupational health and IPC policies and protocols, including the correct use of personal protective equipment, maintaining a safe work environment, and ensuring adherence to cleaning schedules and protocols.

Fig 16: Determinants of HEH



1. **Policies and procedures:**
   Cleaning is a continuous event in the health care setting. To standardize cleaning and disinfection times and to ensure that no surfaces and items are missed during cleaning, health care facilities must have **written procedures** for cleaning and disinfection of care areas and equipment that include :

- The basic principles of infection prevention and control
- Cleaning frequency, clearly defined with schedules, procedures, checklists to ensure no area or items is missed from routine cleaning
- Performance parameters – the expected standard of each item (element) after cleaning
- Defined responsibility/ accountability for cleaning specific items and areas (a list of individual items/categories of items that require cleaning); coordination between cleaning services, ward/unit staff and the IPC team is critical
- Routine and discharge/transfer/terminal cleaning; especially environmental decontamination following the transfer, discharge or death of a colonised or infected patient
- Cleaning in construction/renovation areas
- Cleaning and disinfecting areas under Additional Precautions
- Outbreak management
  - Routine audit and feedback procedures: compliance with environmental cleaning protocols of the immediate surrounding area (that is, the 'patient zone') of patients colonized or infected with CRE-CRAB-CRPsA should be measured and reported regularly.

Health care facilities must review policies and procedures for environmental cleaning on a regular basis.

2. **General cleaning:**

A. Fundamentals
(Following the general principles, published by Assadian et al 2021 (12)

- Focus on areas with the greatest risk of transmission of infection, as patients in these areas (1) are very susceptible to infection (i.e. are immune-compromised and/or have significant comorbidities) and/or (2) are undergoing highly invasive procedures – e.g. operating theatres, intensive care units, delivery suites.

- **Contamination of surfaces after terminal cleaning of isolation rooms results in risk of acquisition by patients subsequently admitted to the same room (intervention: improve terminal room cleaning and disinfection);**
- Contamination of surfaces in isolation rooms results in risk for contamination of health care personnel hands (intervention: daily disinfection of high-touch surfaces);
- Contamination of portable equipment should be tackled by thorough disinfection of portable equipment between patients or use of disposable equipment in isolation rooms;
- Contamination of surfaces in rooms of unidentified carriers of health care-associated pathogens can be mitigated by routine daily cleaning with high standards.
- Cleaning should always start from the least soiled (cleanest) to the most soiled areas (dirtiest) and from the highest point towards the lowest level so that debris may fall on the floor, or from the outside to the inside and is cleaned in a systematic manner to avoid missing any areas.
- Cleaning and disinfection should be performed at least daily and more frequently if the risk of environmental contamination is higher (e.g., intensive care units).
- Emphasize the importance of keeping floors clean and dry. Floor cleaning should be performed last. Place warning signs before starting floor.
- Prioritize the efforts of hospital cleaning staff on the patient zone and high frequency touch surfaces.
- Wipe systematically; follow the principle “one wipe, one site, one direction”
- Use a clean/different cloth or wipe for each patient zone (e.g. bed) and throw away wipes/cloths or dispose of them for reprocessing after each site or when visibly dirty.
- Do not double-dip cloths (not dipping a soiled cloth into the disinfectant solution) or leave cloths soaking in solution.
- Follow proper procedures for effective uses of mops, cloths, and solution.
- Be aware of cross-contamination (e.g. between gloves and cloths) and change cloths frequently.
- Use detergent to remove soil and disinfectant to kill germs. Detergent and water are adequate for cleaning surfaces in nonpatient-care areas (e.g., administrative offices). Remove soil with detergent before using disinfectant if required.***The use of disinfectants as part of routine cleaning is only recommended for: extreme risk areas, as part of outbreak management, terminal cleaning following a MDRO/ infectious diseases, toilets.***
- Daily disinfection of high-touch surfaces: may be useful in isolation rooms to reduce the risk of contamination of the hands of health care personnel providing care for the patients.
- Use freshly prepared and diluted cleaning fluids according to manufacturer’s instructions and change frequently to avoid cross-contamination. The use of recommended concentrations of disinfectant is important. Too high and/or too low concentrations reduce their effectiveness and high concentrations may damage surfaces. This can be achieved by ensuring proper dilution of the disinfectant frequently changing the disinfectant solution and wiping cloths, and regular cleaning and disinfection of cleaning equipment.
- A disinfectant must be in contact with a surface for a specified time and the surface needs to remain wet for that time. Staff should know the contact times for the disinfectants in use locally.
- Cleaning solutions and equipment must be discarded/laundered immediately after cleaning areas with suspected/confirmed MDROs. Bucket solutions become contaminated almost immediately during cleaning and the continued use of the solution transfers increasing numbers of microorganisms to each subsequent surface to be cleaned. Thus, detergent and/or disinfectant solutions must be discarded after each use in areas with suspected/confirmed MDROs and it is essential that a fresh cleaning solution be made daily.(13)
- Clean bathrooms after cleaning the patient room: start with sink, then the grid, continue with shower/bath, and clean toilet last. Areas where faecal contamination is highest, such as sluices and toilets (high contamination risk surfaces), must be cleaned regularly and kept dry as far as possible to prevent biofilm formation
- Always use a new cloth between sink, shower/bath and toilet

- The thorough cleaning of the patient zone(s) of patients colonized or infected with MDRO should be scheduled after cleaning other patient zones (that is, isolation areas should be cleaned after non-isolation areas). No cleaning schedule can be expected to eliminate CPE reliably whilst a colonised or infected patient is present.
- Hospital cleaning staff should respect additional precautions, wearing gowns, mask and goggles as required, and perform hand hygiene at the right moments, including after glove removal.
- Handwash basins should only be used for hand hygiene and not for:
  - disposal of body fluids
  - disposal of tea, coffee or other nutrient containing beverages
  - disposal of IV fluids
  - washing any patient equipment
  - storage of used equipment awaiting decontamination
- Clean walls, blinds, and window curtains in patient-care areas when they are visibly dusty or soiled.

B. Surface cleaning

Housekeeping surfaces can be divided into two groups – those with minimal hand-contact (e.g., floors, and ceilings) and those with frequent hand-contact ("high touch surfaces").

Housekeeping surfaces need to be cleaned only with soap and water or a detergent/disinfectant, depending on the nature of the surface and the type and degree of contamination. The actual physical removal of microorganisms and soil by wiping or scrubbing is probably as important, if not more so, than any antimicrobial effect of the cleaning agent used.

Large and flat surfaces should be cleaned using an S shape motion, starting at the point furthest away then overlapping slightly but without going back over the area to avoid recontamination. Surfaces are unlikely to present an infection risk if they are maintained cleaned and dry.

Removal of biofilms through routine cleaning with a focus on high frequency hand touch surfaces will reduce much of the risk of MDRO transmission. High-touch surfaces in care areas require more frequent cleaning and disinfection than minimal contact surfaces.

C. Patient equipment

This paragraph is addressing the cleaning and disinfection of noncritical equipment and devices that only come into contact with intact patient's skin or the environment.

All staff should take responsibility for the areas in which they work to ensure that patient equipment is managed. It is recommended that every hospital should devise an alphabetised listing (checklist) of all patient equipment indicating the item, the method of decontamination and the staff member responsible for it.

Managers must ensure that staff performing decontamination duties receive training appropriate to the equipment and practices within individual departments. Choice of cleaning materials and cleaning chemical products must be discussed with the local infection control team.

Patient equipment should be cleaned after each use, on a routine schedule basis, but more frequently when visibly dirty, immediately when spillages or contamination with blood or body fluids occur and obviously on patient discharge.

The choice of decontamination method is related to the infection risk associated with the intended use but also the nature of contamination, the time required for processing, the heat, pressure, moisture and chemical tolerance, the availability of the processing equipment, the quality and risk associated with the decontamination method and the manufacturer's guidance.

In case of MDROs, use of detergent/ disinfectant is recommended, in contrary to general equipment where detergent and water is generally suitable. Damp dusting is the best way to clean equipment that cannot be immersed.

Use barrier protective coverings as appropriate for noncritical surfaces that are 1) touched frequently with gloved hands during the delivery of patient care; 2) likely to become contaminated with blood or body substances; or 3) difficult to clean (e.g., computer keyboards).

D. Frequency of cleaning

The cleaning schedule should consider 1) infection risk level (type of pathogens; vulnerability of population to environmental infection and potential for exposure) 2) type of activity 3) level of activity undertaken. Frequency can vary in different contexts and therefore the emphasis must be on risk assessment. Written clear cleaning schedules (clear written rationale and risk assessment for frequencies) must be developed and clearly defined, available to all cleaners.

- High-touch surfaces and items (e.g., doorknobs, bed rails, light switches, and surfaces in and around toilets in patients' rooms) require more frequent cleaning and disinfection than low-touch surfaces and items.
- Surfaces and items in proximity to vulnerable patient require more frequent cleaning and disinfection than surfaces and items in proximity to less vulnerable patients.
- Heavily contaminated surfaces, items and equipment require more frequent cleaning than moderately contaminated surfaces, items and equipment, which in turn require more frequent cleaning and disinfection than lightly contaminated or non-contaminated surfaces, items and equipment.

A set of safe cleaning frequencies cannot meet every healthcare organization's needs and is therefore inappropriate. It would also stifle healthcare organization's ability to allocate cleaning resources where they are most needed, and potentially compromise the requirement to give clinical teams more control in terms of agreeing where available cleaning services are best deployed.

Examples of risk categories for environmental cleaning:

Risk category	Examples
Extreme	ICU units, transplant units, clean room (cell therapy laboratory and aseptic preparation conditions pharmacy)…
High	General wards, pharmacy clean areas…
Medium	Outpatient clinics, day activity areas, medical imaging…
Low	Administrative offices, corridors…

3. Training /structured education:

Staff performing cleaning duties should have a basic understanding of IPC principles and be able to recognize IPC signage. Initial training of the new cleaning staff is essential but refresher training is also required to offer continuous education.

We recommend educating cleaning personnel about the impact of environmental hygiene on MDRO transmission and HAI, as well as the role of objects in disseminating pathogens to the environment and to patients. Clarifying the role and responsibilities of the staff is key.

Cleaners should:

- be familiar with local policies
- be well trained how to make meticulously any cleaning/disinfecting solutions in line with manufacturers' instructions.
- know how to store unused product and how to dispose of it safely.
- understand the protective equipment needed such as wearing the appropriate PPE.

A significant aspect of training is also to develop a hygiene culture among all hospital staff, raising the importance of hygiene and promoting a team approach toward health environmental hygiene.

4. Human resources

Adequately staffed environmental service departments are one of the most important factors that govern the success of environmental cleaning in a health care setting. Under-resourced cleaning staff

increases the risk of HAI, antibiotic-resistant organism transmission and outbreaks. Dedicated environmental service workers are preferred and staff permanently attached to a ward allow the delivering of best cleaning services. Cleaners need to feel part of a ward team, feel that their voice is heard, that their contribution makes a difference to patients, visitors and staff. It is on the other side crucial that ward manager can direct/influence cleaning services to where they are required as part of infection prevention and control activities such as for example in case of emergency cleaning required
It is necessary to clarify the role between the nursing team and cleaners over allocation of cleaning areas and item and to assign responsibility for specific cleaning functions (cleaning responsibility framework). Traceability is necessary: oral transmission or written documentation (computerized) is required to allow information between cleaners, nursing team.
Healthcare establishments must produce a local schedule of cleaning responsibilities detailing all items to be cleaned. This must allow enough time to complete specific tasks.

5. Products & supplies

This includes mops, buckets, cleaning cloths and cleaning solutions. To keep protocols simple, it is important to select a minimum number of different types of disinfectants and products. Many different products with different dilution protocols increase the chance of misunderstanding and errors during the process. A limited number of different products simplify the cleaning process, minimize the training requirements for environmental service workers.
These products should be used as per the manufacturer's instructions and approved by regulatory authorities. Local policy should outline where, when detergent and water are enough, and where a detergent and disinfectant (or combined cleaning and disinfecting agent) are required.

Use a disinfectant that is effective against Gram-negative bacteria. The choice of disinfection will depend on local considerations such as material compatibility and user acceptability. Use a one-step process and a registered hospital detergent/disinfectant designed for general housekeeping purposes in patient-care areas where 1) uncertainty exists as to the nature of the soil on the surfaces (e.g., blood or body fluid contamination versus routine dust or dirt); or 2) uncertainty exists regarding the presence of multidrug resistant organisms on such surfaces.

There is limited evidence on the specific use of non-contact disinfection (hydrogen peroxide dispersal or UV) as the sole intervention. If non-contact disinfection is used, conventional environmental cleaning must occur first to remove surface physical soiling, followed by environmental disinfection.

Items of cleaning equipment that are designated for single-use only should be appropriately disposed of immediately after use. Items that can be reused should be cleaned and stored as per the manufacturer's instructions.
The cleaning or storage room should be dedicated to this activity allowing to clean the equipment used and to store products and supplies. It is important to separate the "clean" area from the "dirty" area for equipment maintenance.
The cleaning trolley should be well organised, tailored to user needs and have a regular maintenance/servicing.

Responsibility

- Hospital cleaning staff (Environmental services staff)
- Cleaning managers
- Healthcare facility administrator/ hospital managers
- Ward clinical staff: nurse, nurse-helper doing routine cleaning in the patient zone; physician in-charge
- Infection prevention and control team
- Patient & family

Procedures and steps

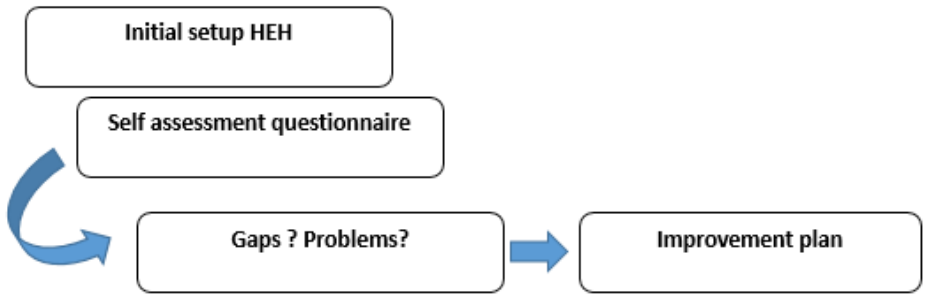
This SOP will provide a guidance on cleaning requirements, *the standards to reach (optimum level),* and a framework for auditing and monitoring. The objective of the intervention is to improve or maintain high standard of cleanliness in all the facilities especially on high-risk wards or throughout the facility for MDROs carriers.

Timeframe

Bundle HEH	Month 1	M2-M6	M7-12	M13-18	M19-24
Self-assessment questionnaire	x				
Improvement plan		x	x		
Improvement initiative ex: training		x	x	x	x
Monitoring Audit		x	x	x	x

First, a self-assessment of HEH (Appendix 1) in the institution is proposed. The self-assessment is only a supporting tool to the participating hospitals, helping to understand the current situation. The first step is to analyze the different issues if present and identify the gaps in the HEH. Defining how to tackle these issues, and determining corrective actions with clear timeframes will be realized by the IPC local team in collaboration with the cleaning management and will depend very much of the particular organization.

Fig 167



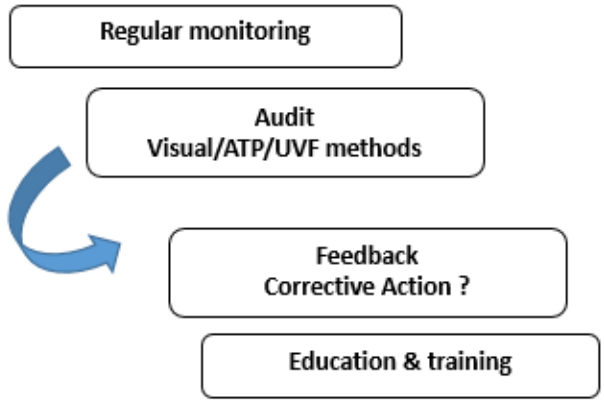
The findings of the self-assessment should be used to develop an improvement plan (Appendix 2), which may include further training, investment in new equipment and materials, enhanced supervision, increased resources, changing the times of cleaning, performance management, development of new protocols or checklists, designation of responsibility for cleaning of specific items, etc.
Among the available tools, organizations will need to determine which elements are applicable to their setting and use it appropriately. Participating hospitals will need to assess the implications and agree on an implementation plan on an individual basis.

Monitoring, evaluation and feedback

Monitoring with regular audits from line supervisory staff such as cleaning managers or ward managers should form part of the daily supervision of cleaning services, providing clear evidence that cleanliness standards are being met safely and responsibly, and where/when they are not, identify any area of

non-compliance and areas for improvement. Cleaning audits also facilitate education programs and motivate staff to thrive for improvements in routine cleaning practices.

Fig 17: Monitoring



Individuals who are responsible for auditing should:

- Have a detailed knowledge of cleaning standards and the cleaning processes (risk areas, frequency…)
- Be part of the cleaning services or infection control team (multidisciplinary team is an asset)
- Be trained in auditing of environmental cleaning, trying to ensure consistency(annual training)
- Not belong to the area that they are auditing if possible
- Be able to make informed judgements of risk and understand the frequencies required to meet cleaning standards in different environments

It is important to assess both routine cleaning and discharge/terminal cleaning. Audits should be randomly undertaken at different times without warning in advanced the cleaner but with consideration for the frequency of cleaning and cleaning schedule. The appropriate frequency of audits have not been determined. Auditing at least twice yearly each cleaner working in the patient's area should be considered as a minimum. But the audit frequency should be reviewed regularly to meet the best frequency to monitor safe cleaning standard for each area. Higher risk areas require increased frequency of cleaning and in turn environmental cleaning in these areas should be audit more frequently.

Audit results must be collected, presented and discussed with the cleaning management of the health care facility and even with relevant hospital governance.

3. Technical audit:

Evaluations and audits of cleaning can be performed through a variety of different methods. There is no consensus on the best method to assess hospital cleanliness. This is due to the fact it is unknown how clean surfaces must be in order to prevent HAIs (14).

The minimum audit method recommended in REVERSE project is visual assessment. And if available, ultraviolet fluorescent marker or adenosine triphosphate method can be used. We do not recommend microbiological cultures as a routine monitoring method.

The focus should be on patient care areas such as inpatient bed areas (especially medical, surgical, transplant, ICU units enrolled in REVERSE project). The pedagogical impact of this type of evaluation allows continuous awareness of compliance with protocols.

In the room, it is crucial to focus on high frequently touched surfaces:

- light switches/plastic pulls
- taps, dispensers, toilet flush handles
- door handles and push plates
- over-bed table and trays
- bed rails
- grab rails
- patient chair arms and seat
- relevant parts of notes, linen, drug and general-purpose trolleys
- nurse call buttons
- patient entertainment system, including any TV remote controls
- bedside drawers and locker handles
- kitchen cupboard handles
- patient area multi-user phones and computer buttons and receiver

Different types of methodologies:
Process evaluation:
A. visual inspection/ direct observation of cleaning practices
Visual assessment consists on a visual inspection of the cleanliness of the premises and equipment by the audit responsible person, immediately after cleaning by the employee and in his presence. The visual inspection takes into account the following factors:

- the amount of visible dust
- Stains visible on a surface
- footprints or streaks from rolling stock on the ground
- any other “non-standard” observation

It is the cheapest, simplest and quickest of all methods described in this SOP, evaluating all surfaces for gross deficiencies. Visual assessment of the cleanliness of a hospital ward, surface or item may satisfy aesthetic obligations. But it is not a proxy for decontamination, not reliably assessing the infection risk posed to patients. Another clear disadvantage is that it is subjective, dependent of each observer with high variability and also relatively time consuming.

B. Fluorescent gel/fluorescent marker method
Fluorescent gel dotes are applied to key surfaces and object prior to cleaning; after cleaning, any area not properly cleaned is detected using fluorescence under ultraviolet light. This method is quick, objective and requires minimal training. However it focuses mostly on the surfaces and objects to clean but does not assess bioburden (consequently the technique of cleaning). It is quite labor intensive as surfaces must be marked before cleaning.

Outcome process:

C. ATP bioluminescence
The adenosine triphosphate (ATP) method consists of using a luminometer, a device that detects, after swabbing a selected surface, ATP from bacteria, yeast, mold but also any organic material. It is a quick, objective quantitative method, providing immediate feedback and requiring minimal training (15, 16). However, there are different commercial ATP devices with different threshold levels (no standardization).
There is also a risk of aberrant results due to organic soil, disinfectants and cleaning materials. ATP systems clearly encourage cleaning effectiveness (17), seems to be better accepted by staff as a feedback method, given the perceived subjectivity of visual assessments (18).

D. Microbiological cultures

Routine environmental cultures are not recommended except in the context of an outbreak investigation, suggesting for example an environmental reservoir as source of an outbreak. The rates of healthcare–associated infection had not been associated with a clear level of general microbial contamination of environmental surfaces, and meaningful standards for permissible levels of microbial contamination of environmental surfaces do not exist. Moreover microbiologic sampling is an expensive and time-consuming process, requiring laboratory resources, and expert interpretation of results.

4. **Efficacy audit***:*

The efficacy audit is assessing the cleaning process. It is a management tool to ensure that correct cleaning procedures are delivered. It is mainly used to observe the methodology of cleaning, the wear of correct uniform, the respect of additional precautions, and the use of products and materials appropriately. (see Appendix 3)

5. Feedbacks

Feedbacks following an audit are essential to the cleaners, highlighting any problems and consequently allowing corrective action (with regard to the risk category of the area, the type of non-compliance identified and the availability of the appropriate staff and equipment to rectify the issue).
Immediate feedback following the audit is an essential tool to improve the quality of cleaning.

Material and Resources (REVERSE project)

- Self- assessment questionnaire (Appendix 1)



Appendix 1
Self-assessment ques

- Cleaning responsibilities framework (Appendix 2)



Appendix 2
cleaning responsibilit

- Audit tool (Appendix 3)



Appendix 3 Audit
tool.docx

- Disinfectant selection (Appendix 4)



Appendix 4
Disinfectant selection

- Improvement plan (Appendix 5)



Appendix 5
Improvement plan.dc

- Poster Benefits of cleaning (Appendix 6)



Appendix 6 Poster
Benefits of cleaning.p

- Training example



Appendix 7
Cleaning training.ppt

HEH activities minimum

- Healthcare Environmental Hygiene Self-Assessment:
  - realized once at the beginning of intervention
- Development of improvement plan
- Audit frequency minimum requirement 2x/ year for each cleaner (local tool or REVERSE tool) in the REVERSE units

References:

1. Tacconelli E, Cataldo MA, Dancer SJ, De Angelis G, Falcone M, Frank U, et al. ESCMID guidelines for the management of the infection control measures to reduce transmission of multidrug-resistant Gram-negative bacteria in hospitalized patients. Clin Microbiol Infect. 2014;20 Suppl 1:1-55.
2. Mitchell BG, Hall L, White N, Barnett AG, Halton K, Paterson DL, et al. An environmental cleaning bundle and health-care-associated infections in hospitals (REACH): a multicentre, randomised trial. Lancet Infect Dis. 2019;19(4):410-8.
3. Peters A, Schmid MN, Parneix P, Lebowitz D, de Kraker M, Sauser J, et al. Impact of environmental hygiene interventions on healthcare-associated infections and patient colonization: a systematic review. Antimicrob Resist Infect Control. 2022;11(1):38.
4. Dancer SJ. Hospital cleaning in the 21st century. Eur J Clin Microbiol Infect Dis. 2011;30(12):1473-81.
5. WHO guidelines for the prevention and control of carbapenem-resistant Enterobacteriaceae, Acinetobacter baumannii and Pseudomonas aeruginosa in healthcare facilities. 2017.
6. Ontario Ph. Best practives for environmental cleaning for Prevention and Control of Infections in All Healthcare settings. April 2018.
7. NHS. National Standards of Healthcare cleanliness 2021.
8. CDC. Guidelines for Environmental infection control in Health-care facilities. Updated July 2019.
9. Hall L, Farrington A, Mitchell BG, Barnett AG, Halton K, Allen M, et al. Researching effective approaches to cleaning in hospitals: protocol of the REACH study, a multi-site stepped-wedge randomised trial. Implement Sci. 2016;11:44.
10. Executive IHS. Cleaning Manual-Acute Hospitals.
11. policy Nh. Cleaning of healthcare environment. 2020.
12. Assadian O, Harbarth S, Vos M, Knobloch JK, Asensio A, Widmer AF. Practical recommendations for routine cleaning and disinfection procedures in healthcare institutions: a narrative review. J Hosp Infect. 2021;113:104-14.
13. 2019 WHO. WHO_Implementation manual to prevent and control the spread of carbapenem-resistant organisms at the national and health care facility level.
14. Doll M, Stevens M, Bearman G. Environmental cleaning and disinfection of patient areas. Int J Infect Dis. 2018;67:52-7.
15. Deshpande A, Dunn AN, Fox J, Cadnum JL, Mana TSC, Jencson A, et al. Monitoring the effectiveness of daily cleaning practices in an intensive care unit (ICU) setting using an adenosine triphosphate (ATP) bioluminescence assay. Am J Infect Control. 2020;48(7):757-60.
16. Mitchell BG, McGhie A, Whiteley G, Farrington A, Hall L, Halton K, et al. Evaluating bio-burden of frequently touched surfaces using Adenosine Triphosphate bioluminescence (ATP): Results from the Researching Effective Approaches to Cleaning in Hospitals (REACH) trial. Infect Dis Health. 2020;25(3):168-74.
17. Ziegler MJ, Babcock HH, Welbel SF, Warren DK, Trick WE, Tolomeo P, et al. Stopping Hospital Infections with Environmental Services (SHINE): A Cluster-Randomized Trial of Intensive Monitoring Methods for Terminal Room Cleaning on Rates of Multidrug-Resistant Organisms in the Intensive Care Unit. Clin Infect Dis. 2022.
18. Knape L, Hambraeus A, Lytsy B. The adenosine triphosphate method as a quality control tool to assess 'cleanliness' of frequently touched hospital surfaces. J Hosp Infect. 2015;91(2):166-70.

Environmental sampling

Title	Environmental sampling
Document status	Approved by on
Version Number	1.2
Authors	Amir Nutman, Yehuda Carmeli

Introduction

The healthcare environment may be contaminated by multidrug-resistant Gram-negative bacteria (MDR-GNB), either directly from infected or colonized patients, or indirectly by healthcare workers' hands. Environmental contamination plays a role in transmission of MDR-GNB (Wilson *et al.*, 2016). For example, admission to an ICU room previously occupied by patients infected or colonized with *A. baumannii* or *P. aeruginosa* presents an increased risk for acquiring these organisms (Nseir *et al.*, 2011). In an analysis of over 1,500 outbreak investigations, the environment was the source in almost 20% of outbreaks, and contaminated equipment in 21% (Gastmeier *et al.*, 2006).
However, evidence supporting the use of environmental sampling for MDR-GNB to reduce the spread of these pathogens is limited, and it is often implemented with enhanced cleaning strategies (Word Health Organization, 2017). Furthermore, performing environmental sampling is challenging, as there are no standardised microbiological methods and no clear benchmark for interpreting the results. Therefore, most guidelines do not recommended routine environmental sampling as part of basic infection control measures (Tacconelli *et al.*, 2014; Wilson *et al.*, 2016; Word Health Organization, 2017).
In outbreak settings, environmental sampling may locate a possible common source for the outbreak or reveal that cleaning has failed to remove the outbreak strain from the environment (Tacconelli *et al.*, 2014; Wilson *et al.*, 2016). In non-outbreak settings, environmental sampling can be used to evaluate cleaning processes, such as after adopting a new cleaning product or policy. Environmental sampling may also be used for research purposes to study potential environmental reservoirs and survival of MDR-GNB in different settings (Centers for Disease Control and Prevention, 2019).

Scope

This policy document provides guidance on environmental sampling to all the participating hospitals in the REVERSE project. The objective of this document is to support the implementation of environmental sampling;

By offering:

- Guidance on *when* to consider environmental sampling.
- Guidance on *where* to perform environmental sampling.
- Guidance on *how* to perform environmental sampling (sample collection, culture and interpretation).

By proposing:

- Writing an institutional protocol for sample collection, processing and interpretation of results.

General principles and definitions

- **MDR-GNB** – Carbapenem-resistant *Enterobacterales* (CRE), carbapenem-resistant *Acinetobacter baumannii* (CRAB), and carbapenem-resistant *Pseudomonas aeruginosa* (CRPA)
- **MDR-GNB carrier** – A patient from whom an MDR-GNB was isolated, by either screening cultures or clinical samples.
- **Patient zone** – The immediate surroundings (space and objects) around a patient that may be touched by the patient and/or healthcare workers. This area is likely to be contaminated by the patient's bacteria.
- **High-touch surfaces** – Surfaces and items that have frequent contact with the hands of healthcare workers, patients and/or visitors. These surfaces may be in the patient zone (mattress, bedrails, bedside table, call bell, monitor, infusion pump, privacy curtain, etc.), as well as outside the patient zone (such as doorknobs, light switches and computer keyboards).

Procedures and steps

When to consider environmental sampling

- Non-outbreak settings:
  - When a new cleaning protocol (or product) is adopted, to evaluate its effectiveness at eliminating or reducing the load of a specific MDR-GNB in the patient zone and high-touch surfaces.
  - To monitor cleaning processes, such as terminal cleaning in rooms after discharge of an MDR-GNB carrier (usually performed as part of enhanced cleaning strategies).
- Outbreak settings:
  - To support investigation of an outbreak of MDR-GNB when environmental reservoirs are implicated epidemiologically in transmission.
  - When failure of routine cleaning practices, especially of the patient zone, is suspected as a cause for ongoing transmission of MDR-GNB.
  - To detect a common source of transmission in the healthcare environment, usually outside the patient zone. An environmental source may include fomites (such as medical equipment), air and water.
- Research settings:
  - To study the spread of MDR-GNB in the healthcare environment, including potential environmental reservoirs and survival of MDR-GNB under normal or simulated conditions.

Where to perform environmental sampling

Targeted sampling according to a defined protocol is preferred over random, undirected sampling (Centers for Disease Control and Prevention, 2019).

Since sampling can only reflect a very small fraction of the healthcare environment, the general approach should be to choose high-touch sites that are likely to be relevant for cross-transmission (Wilson *et al.*, 2016). In outbreak settings, sampling should also include shared equipment (such as blood pressure measurement devices, bedside ultrasound devices or portable x-ray carts), hand-hygiene sinks, and common areas such as clean linen and storage rooms. In the ICU, sampling should include respiratory equipment (Wilson *et al.*, 2016).

Indoor air may be contaminated with MDR-GNB, especially in the vicinity of carriers (Mousa *et al.*, 2019). There are many factors that determine the survival and dispersion of MDR-GNB in bio-aerosols including temperature and relative humidity, air-handling systems, target organism, size and concentration of particles, and specific aerosol generating procedures (Centers for Disease Control and Prevention, 2019).

Water systems may become an environmental reservoir for both CRPA and CRE and lead to ongoing transmission. When contamination of the water system is investigated, three different sources should be considered: 1) Contamination of the water supply. Contamination with MDR-GNB usually represents a problem in the local (ward, wing or building) water pipe system or in water chlorination. Outbreaks usually involve multiple units. 2) Faucet contamination. This may occurs due to splashes from contaminated hands or fluids poured into the sinks. 3) Drain contamination. This may be an unavoidable condition (from washing contaminated hands or equipment), however it may lead to contamination of healthcare workers' hands, when sinks are not designed properly, and splashes from the drain occur during handwashing. Sampling of the water system needs to address all these possibilities and be conducted accordingly. Routine sampling of potable water should be conducted according to local regulations and the healthcare facility water safety plan.

How to perform environmental sampling and interpret results

The infection control team should coordinate environmental sampling with the microbiology laboratory. The aim should be clearly defined, and there should be a defined protocol for sample collection (including method, location and number of samples to be collected), sample processing in the microbiological laboratory, and interpretation of results.

There are both direct and indirect methods for environmental surface sampling (Rawlinson, Ciric and Cloutman-Green, 2019). Direct methods are self-enclosed sampling devices, such as contact plates and dipslides, which can be pressed directly on to a surface, and do not require further processing in the laboratory. They are more suitable for flat and dry surfaces. Direct methods provide semi-quantitative results in the form of colony counts. Sampling can be performed with selective or non-selective media, depending on the organism to be recovered. Indirect methods, such as swabs, gauze pads and sponges, are suitable for both dry and wet surfaces (e.g. faucets and drains), and can be manipulated around uneven surfaces (e.g. bedrails and doorknobs). However, they are more difficult to process in the laboratory since they require an extraction step. They are also more difficult to standardize, as bacterial counts depend on the sampling area, pattern and pressure during sampling. These methods are more suitable for detection of target MDR-GNB, rather than determining surface "bacterial load". Sponges can sample large surface areas with ease, and have shown better recovery rates from a variety of surface materials including fabrics. Yield is improved by pre-moistening with a neutralizing agent (especially when residual disinfectants are expected on the surfaces). When using indirect sampling methods, sample processing may include direct plating on agar, an enrichment step before plating, and be subject to either culture and/or molecular processing. Both selective or non-selective media may be used (Rawlinson, Ciric and Cloutman-Green, 2019).

Air sampling methods include sedimentation on settle plates (using selective or non-selective agar media), and specific air-sampling devices (such as liquid impingment and solid impactor samplers). A detailed discussion of air sampling instruments and sampling process is beyond the scope of this document, and may be found elsewhere (Centers for Disease Control and Prevention, 2019).

Sampling water systems to support an outbreak investigation: faucets can be sampled with swabs or sponges (positive results may represent faucet or water contamination). Drains can be sampled with swabs. Potable water can be sampled from a sampling port in the water supply system. Sampling water from a faucet requires disinfection of the faucet and flushing of the water line (hot and then cold water) before sample collection; attachments (e.g. screens and aerators) should be removed. An appropriate volume of water should be collected ($\geq$ 100 ml), and neutralization of residual chlorine and chelation of heavy metals is needed to recover waterborne pathogens. If bacterial counts are expected to be low, a large volume of water can be filtered through a membrane, which can be applied directly onto the surface of an agar plate (Centers for Disease Control and Prevention, 2019).

Environmental sampling, as with all laboratory testing, should not be conducted if there is no plan for interpreting and acting on the results. Molecular typing and comparison of MDR-GNB isolated from the environment with clinical isolates should be conducted when possible (Centers for Disease Control and Prevention, 2019).

Negative results should be interpreted with caution, as these represent only the surfaces sampled and are influenced by sampling and laboratory techniques. When sampling for a specific pathogen, a negative result may not necessarily mean a clean and safe environment for the patient; the main value is when a positive result is found, which may direct interventions.

Material, Resources & Responsibilities

- Infection control team and clinical microbiologists – writing an institutional protocol for environmental sampling.
- Administration – providing the resources (human and material) to conduct environmental sampling.
- Infection control team – implementation of environmental sampling as needed according to the defined protocol.

Monitoring and Evaluation

- Institutional multidisciplinary protocol for environmental sampling. This protocol should define:
  - Targeted sample collection in specific settings
  - Laboratory methods for culturing
  - Interpretation of results
  - Expected actions based on the results

Appendix

Video demonstrating environmental surface sampling with sponge-wipes:

- https://youtu.be/NPGJFLW0w7U (from 02:33).

References

Centers for Disease Control and Prevention (2019) *Healthcare Infection Control Practices Advisory Committee (HICPAC): Guidelines for Environmental Infection Control in Health-Care Facilities*, *U.S. Department of Health and Human Services Centers for Disease Control and Prevention (CDC) Atlanta, GA 30329*. Available at: http://www.cdc.gov/hicpac/pdf/guidelines/eic_in_hcf_03.pdf.

Gastmeier, P. *et al.* (2006) 'Where should one search when confronted with outbreaks of nosocomial infection?', *American Journal of Infection Control*, 34(9), pp. 603–605. doi: 10.1016/j.ajic.2006.01.014.

Mousa, M. *et al.* (2019) 'Droplet aerosol dissemination of carbapenem-resistant Acinetobacter baumannii surrounding ventilated patients', *Infection Control and Hospital Epidemiology*, 40(3), pp. 365–367. doi: 10.1017/ice.2018.335.

Nseir, S. *et al.* (2011) 'Risk of acquiring multidrug-resistant Gram-negative bacilli from prior room occupants in the intensive care unit', *Clinical Microbiology and Infection*, 17(8), pp. 1201–1208. doi: 10.1111/j.1469-0691.2010.03420.x.

Rawlinson, S., Ciric, L. and Cloutman-Green, E. (2019) 'How to carry out microbiological sampling of healthcare environment surfaces? A review of current evidence', *Journal of Hospital Infection*, pp. 363–374. doi: 10.1016/j.jhin.2019.07.015.

Tacconelli, E. *et al.* (2014) 'ESCMID guidelines for the management of the infection control measures to reduce transmission of multidrug-resistant Gram-negative bacteria in hospitalized patients', *Clinical Microbiology and Infection*, 20(S1), pp. 1–55. doi: 10.1111/1469-0691.12427.

Wilson, A. P. R. *et al.* (2016) 'Prevention and control of multi-drug-resistant Gram-negative bacteria: Recommendations from a Joint Working Party', *Journal of Hospital Infection*, pp. S1–S44. doi: 10.1016/j.jhin.2015.08.007.

Word Health Organization (2017) *Guidelines for the Prevention and Control of Carbapenem-Resistant Enterobacteriaceae, Acinetobacter baumannii and Pseudomonas aeruginosa in Health Care Facilities*, *WHO Document Production Services, Geneva, Switzerland Cover*.

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1. Introduction and Background

1.1 Role of ABS in combating AMR

Hospital-acquired infections (HAIs) due to multidrug-resistant organisms (MDRO) constitute a significant threat to human health, and interventions to reduce the overuse of antibiotics are necessary. Quality improvement strategies to optimize antibiotic prescriptions are recommended as part of multifaceted interventions to tackle antimicrobial resistance (AMR). The World Helath Organization defines antibiotic stewardship (ABS) as a coherent set of integrated actions to promote antimicrobials' responsible and appropriate use[1]. Education, auditing, restriction of broad-spectrum antibiotics, shortening of treatment duration, antibiotic cycling or mixing, personalized antibiotic prophylaxis, and customized guidelines based on national and local susceptibility data are just some examples of possible components of ABS strategies. In real life, the two most difficult challenges in applying effective ABS programs are 1) the lack of an accepted gold standard of ABS components and 2) the generalizability of available evidence, as it comes mainly from countries with low AMR prevalence. It is also unclear which combination of the ABS components is most effective, what the most effective strategies for the implementation are, and whether there is a priority order according to the hospital setting. Implementing several of these measures has significantly reduced hospital costs and antibiotic consumption[2]. Several systematic reviews and meta-analyses have successfully reduced *Clostridioides difficile* infections (CDIs) in hospitalized patients through antimicrobial stewardship interventions.[3] Achieved benefits such as favorable clinical outcomes, limited adverse events, and lowered costs have been linked to prescribing appropriate empirical therapy tailored to local epidemiological data, de-escalation, switching from intravenous to oral treatment, therapeutic drug monitoring, antibiotic restriction, and bedside consultation. Guideline-adherent empirical therapy has been associated with a relative risk reduction of 35% of mortality. A recent meta-analysis also showed that implementing ABS reduces infection and colonization due to AMR pathogens and CDI in hospitalized patients. The most significant reductions were reported regarding infections or colonization due to multidrug-resistant Gram-negative bacteria (51% reduction), ESBL-producing Gram-negative bacteria (48%), methicillin-resistant *Staphylococcus aureus* (37%), and CDI (32%). Notably, ABS was highly effective in haematology-oncology wards (59% reduction), and the coimplementation with hand hygiene interventions had an additional benefit on the overall success of reducing resistance by two-thirds. The main goal of the REVERSE ABS program is to produce evidence on the effect of combining two interdependent programs, Infection Prevention and Control (IPC) and ABS, together to achieve the most significant impact. The primary objective of the ABS Work Package is to evaluate whether an ABS program targeting AMR in high MDRO-prevalence settings can reduce total antibiotic consumption by at least 15% without putting patients at risk[4].

[1] World Health Organization. "WHO policy guidance on integrated antimicrobial stewardship activities." (2021).

[2] Zay Ya K, Win PTN, Bielicki J, Lambiris M, Fink G. Association Between Antimicrobial Stewardship Programs and Antibiotic Use Globally: A Systematic Review and Meta-Analysis. JAMA Netw Open. 2023 Feb 1;6(2):e2253806. doi: 10.1001/jamanetworkopen.2022.53806. PMID: 36757700; PMCID: PMC9912134.

[3] Feazel LM, Malhotra A, Perencevich EN, Kaboli P, Diekema DJ, Schweizer ML. Effect of antibiotic stewardship programmes on Clostridium difficile incidence: a systematic review and meta-analysis. J Antimicrob Chemother. 2014 Jul;69(7):1748-54. doi: 10.1093/jac/dku046. Epub 2014 Mar 14. PMID: 24633207.

[4] Baur D, Gladstone BP, Burkert F, Carrara E, Foschi F, Döbele S, Tacconelli E. Effect of antibiotic stewardship on the incidence of infection and colonisation with antibiotic-resistant bacteria and Clostridium difficile infection: a systematic review and meta-analysis. Lancet Infect Dis. 2017 Sep;17(9):990-1001. doi: 10.1016/S1473-3099(17)30325-0. Epub 2017 Jun 16. PMID: 28629876.

1.2 Overview of basic ABS within the REVERSE project

The ABS intervention is stratified into two main programs: 1) a best practice program targeting all the REVERSE hospitals and focusing on organization, structure, and available microbiology services (Basic ABS), and 2) tailored interventions targeting only specific wards in selected hospitals (Advanced or Tailored ABS discussed elsewhere).

The feasibility and success of implementing the basic ABS are strongly linked to relevant key elements that might be already in place at different levels in the REVERSE hospitals. The local key elements for ABS progress are related to the 'ABS leadership and governance' (i.e., presence of national AMR plans and national requirements, presence of a multidisciplinary stewardship team or committee, human resources dedicated to ABS), to existing 'ABS activities' (i.e., presence of guidance documents on syndrome-specific treatment, dedicated recommendations for new drugs, monitoring of prescriptions' appropriateness) and to 'monitoring of antimicrobial use (AMU)' (i.e., antibiotic formulary, a regular report produced by the pharmacy, measure antimicrobial use metrics such as Defined-Daily Doses (DDDs) or Days of therapy (DOTs) stratified by ward, by molecule, by AWaRe class).

The ABS readiness survey conducted in April 2022 and presented during the REVERSE Annual meeting in 2023 provides an overview of the state of the art of ABS in each hospital. Following the REVERSE Master Protocol, site visits will be conducted by WP5 and WP4 members in selected hospitals before the beginning of the implementation phase. Those site visits will allow the project's coordination to observe further and pinpoint potential barriers and facilitators that might act as determinants for successfully implementing the ABS activities. An in-person workshop focused on the ABS intervention and its implementation will be held with participating hospitals (grouped by cohort) before the start of the intervention.

The ABS basic intervention will focus on three major non-restrictive elements: 'education', 'guidelines provision', and 'audit and feedback' (either through written feedback or via antibiotic rounds). Antibiotic consumption (overall and by class) will be measured regularly by ward and used as a process indicator.

1.3 Ethical Approvals

Each hospital has been granted ethical approval at a local level based on the Master Protocol approved by the Swiss ethics committee.

2. ABS Basic Intervention Methodology

2.1 Introduction

2.1.1 ABS definition

One of the most cited definitions of 'Antibiotic Stewardship' refers to 'coordinated interventions designed to improve and measure the appropriate use of antimicrobial agents by promoting the selection of the optimal antimicrobial drug regimen including dosing, duration of therapy, and route of administration' (IDSA, 2012)[5]. This definition underlines the key purpose of the intervention (i.e., targeting all the aspects of antibiotic prescription). Still, it might risk overlooking some inherent challenges of ABS, such as establishing 'what is appropriate' and the fundamental roles of nonprescribers in promoting the 'responsible' use of antibiotics while balancing individual and societal needs.

For this project, we will define ABS as 'a coherent set of actions which promote using antimicrobials responsibly'.[6]

2.1.2 ABS intervention components

The most comprehensive systematic review assessing the efficacy of ABS interventions from a behavior change perspective (Cochrane, 2017) categorized ABS **intervention types or components** as 'restriction' when the **intervention function** implied rules to reduce the opportunity to engage in the target behavior (or increase the target behavior by reducing the chance to engage in competing behaviors) and 'enablement' as increasing means/reducing barriers to increase capability or opportunity. The various intervention components (education, persuasion, restriction, environmental restructuring, and enablement) aim to target prescribers' behaviors and can be categorized according to their intervention function.[7]

The following types of interventions are generally categorized from existing literature as 'enabling interventions':

- Audit and feedback: systematic review of prescribers' performance over a specified period and subsequent feedback to reinforce/modify clinical practice.
- Education: meetings, distribution of educational materials, academic detailing, or review of individual patients with recommendations for change.
- Reminders are provided verbally, on paper, in the workplace environment, or on the computer.
- Structural: changing from paper to computerized records, new technology for rapid microbiology testing or measurement of inflammatory markers.

[5] Fishman, Neil, Society for Healthcare Epidemiology of America, and Infectious Diseases Society of America. "Policy statement on antimicrobial stewardship by the society for healthcare epidemiology of America (SHEA), the infectious diseases society of America (IDSA), and the pediatric infectious diseases society (PIDS)." Infection Control & Hospital Epidemiology 33.4 (2012): 322-327.

[6] Dyar, O. J., et al. "What is antimicrobial stewardship?" Clinical microbiology and infection 23.11 (2017): 793-798.

[7] Davey P, Marwick CA, Scott CL, Charani E, McNeil K, Brown E, Gould IM, Ramsay CR, Michie S. Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database Syst Rev. 2017 Feb 9;2(2):CD003543. doi: 10.1002/14651858.CD003543.pub4. PMID: 28178770; PMCID: PMC6464541.

The following are usually identified as 'restrictive interventions':

- Selective reporting of antimicrobial susceptibilities.
- Formulary restriction requiring prior authorization (expert approval).
- Therapeutic substitution.
- Automatic stop orders.

According to the authors' conclusions, ABS interventions were associated with shorter treatments (high certainty of evidence) and improved adherence to antibiotic policy without affecting the risk of death (moderate certainty of evidence). Some concerns were raised that restrictive interventions may lead to delays in treatment and negative professional culture because of a breakdown in communication and trust between infection specialists and clinical teams (low-certainty evidence). Overall, both enablement and restriction were independently associated with increased compliance with antibiotic policies, and enablement enhanced the effect of restrictive interventions (highcertainty evidence). Enabling interventions that included feedback were probably more effective than those that did not (moderate-certainty evidence).

For the REVERSE ABS program, we selected 'guideline provision' and 'audit and feedback' as the main components of the ABS intervention. No restrictive elements are included in the REVERSE ABS program not to interfere with already existing activities and to avoid the risk of potentially delaying effective treatments. The intervention components will be implemented by the local ABS teams according to the accessibility of antibiotic prescription data and the amount of personnel to be dedicated to ABS activities.

2.1.3 What is the appropriate antibiotic treatment?

The main aim of ABS interventions is to reduce overall antibiotic consumption while focusing on inappropriate use. Therefore, antibiotic stewardship programs should comprise the following distinct metrics for measuring the quantity and quality of antibiotic use to be successful.

2.1.3 a. Antimicrobial consumption data

Antimicrobial consumption data might be easy to obtain through collaboration with the hospital pharmacy. Through some elaboration, antibiotic consumption data can be used to inform ABS intervention (i.e., to target settings with the highest consumption) and as a benchmark to measure the intervention effectiveness with historical data or other healthcare facilities.

The pharmacist can analyze patient-level electronic prescriptions (with the support of the Information Technology department). The following metrics can be applied: [8]

- Defined Daily Doses (DDDs): The assumed average maintenance dose per day for a drug used for its main indication in adults as specified by the World Health Organization (e.g., 1 DDD of Levofloxacin = 500mg).

[8] (https://www.publichealthontario.ca/-/media/documents/A/2017/asp-metrics-examples.pdf).

- Days of Observed Therapy (DOTs): The number of days a patient receives an antimicrobial agent (regardless of dose). Any dose of an antibiotic that is received for 24 hours represents 1 DOT. The DOT for a given patient on multiple antibiotics will be the sum of the DOTs for each antibiotic the patient receives.
- Length of Therapy (LOTs): The number of days a patient receives systemic antimicrobial agents, irrespective of the number of drugs. Therefore, LOT will be lower than or equal to DOT because each antibiotic received is its DOT.
- Antibiotic Free Days (AFDs): The number of days that antimicrobial agents were NOT received during a given period on a given hospital unit. Like LOT, this metric is calculated irrespective of the number of antimicrobial agents received.

DDDs and DOTs are often standardized to 1000 patient days (PDs) to allow comparison between hospitals or services of different sizes. DDDs and DOTs can be stratified by molecule, class, ward, or area. Since DDDs can be influenced by patients' characteristics affecting dosing, the contemporary use of at least one additional metric (DOTs, LOTs, AFDs) is usually recommended to gather more reliable data.

When electronic prescriptions are unavailable in the hospital, antibiotic consumption is generally measured by what the hospital pharmacy dispenses to the wards. In this case, only DDDs can be computed by the pharmacy, and the reliability of the data strongly depends on the hospital organization (how frequently are the orders made? Does each ward order the antibiotics separately? Is stockpiling allowed in the wards?). Measuring DOTs/LOTs/AFDs in those settings usually relies on manual data collection, and it is difficult to perform on a large scale.

2.1.3.b. Quality indicators

Measuring appropriateness of healthcare is typically done using quality indicators (QIs), defined as 'measurable elements of practice performance for which there is evidence or consensus that they can be used to assess the quality, and hence change the quality of care provided'. QIs of appropriate antibiotic use have been identified as valuable tools for ABS interventions to help select targets for improvement and measure the intervention's effectiveness.

There is an abundance of literature relative to QIs for assessing antibiotic prescriptions in hospitalized patients. QIs can capture different aspects of the prescription: from the diagnostic phase to the antibiotic plan, to the selection of the correct infusion route, or the use of pharmacokinetic/pharmacodynamic (PK/PD) targets.

For the REVERSE ABS program, the following QIs have been selected from existing literature based on their relevance and the feasibility of their assessment[9].

[9] Monnier AA, Schouten J, Le Maréchal M, Tebano G, Pulcini C, Stanic Benic M, Vlahovic-Palcevski V, Milanic R, Adriaenssens N, Versporten A, Huttner B, Zanichelli V, Hulscher ME, Gyssens IC; DRIVE-AB WP1 group. Quality indicators for responsible antibiotic use in the inpatient setting: a systematic review followed by an international multidisciplinary consensus procedure. J Antimicrob Chemother. 2018 Jun 1;73(suppl_6):vi30-vi39. doi: 10.1093/jac/dky116. PMID: 29878221; PMCID: PMC5989598.

Guideline adherence in empirical treatment

Empiric antimicrobial therapy is defined as appropriate if the prescription follows guidelines, including antimicrobial choice, dosage and frequency, route, and duration[10]. Empiric antibiotic therapy should have an adequate spectrum, neither too narrow nor too broad, to target the most probable bacterial etiology and their potential resistance. The molecule(s) chosen should be able to reach the suspected site of infection, and the route of administration should be appropriate to the type of infection, the clinical status of the patient, and the patient's allergy history[11]. The impact of appropriate therapy is particularly relevant in severe infections where early *in vitro* coverage has been consistently associated with a survival benefit. Antimicrobial resistance is one of the strongest determinants of inappropriate coverage and, therefore, a risk factor for unfavorable outcomes.[12]

Recommendations for empiric therapy must counterbalance the need for early effectiveness with the risks associated with a too-wide spectrum or increased toxicities. Tailoring the recommendations to local epidemiology has become a growing necessity due to the high variability of antimicrobial resistance rates and mechanisms. In a recent consensus, a threshold of 90% of coverage was recommended for severe infections, whereas the threshold for non-severe infections can be lowered to 75%[13]. With local epidemiology, it is essential to adopt an individual risk-based approach to select the patients who would benefit from a broad-spectrum empirical treatment. For example, the last version of the surviving sepsis campaign guidelines recommended early coverage for MRSA or MDRGram negatives only for patients with specific risk factors[14].

Guideline adherence in surgical prophylaxis

Antibiotic surgical prophylaxis is recommended for procedures where the risk of infectious complications outweighs any potential harm from antibiotic exposure. The appropriateness of surgical prophylaxis is defined according to existing guidelines. It refers to the choice of the antibiotic, the timing of the administration before the surgery, the dose, the repeat administration during the operation, and the overall duration[15]. The appropriateness of surgical antimicrobial prophylaxis is known to be associated with reduced rates of surgical site infections; however, adherence to guidelines (especially in terms of timing and duration) is still low in several contexts. For example, the most recent ECDC point prevalence survey showed that surgical prophylaxis was excessively prolonged for > 1 day in 54% of cases. Also, there was a negative correlation between the percentage of prescriptions changed during treatment (a surrogate for antimicrobial stewardship activities) and the percentage of surgical prophylaxis prescribed for more than one day[16].

[10] James, R. et al. The feasibility and generalizability of assessing the appropriateness of antimicrobial prescribing in hospitals: a review of the Australian National Antimicrobial Prescribing Survey. JAC-Antimicrobial Resist. 4, (2022).
[11] Dresser, L. D. et al. Use of a structured panel process to define antimicrobial prescribing appropriateness in critical care. J. Antimicrob. Chemother. 73, 246–249 (2018).
[12] Kadri, S. S. et al. Inappropriate empirical antibiotic therapy for bloodstream infections based on discordant in-vitro susceptibilities: a retrospective cohort analysis of prevalence, predictors, and mortality risk in US hospitals. Lancet Infect. Dis. 21, 241–251 (2021).
[13] Pezzani, Maria Diletta, et al. "Linking antimicrobial resistance surveillance to antibiotic policy in healthcare settings: the COMBACTEMagnet EPI-Net COACH project." Journal of Antimicrobial Chemotherapy 75. Supplement_2 (2020): ii2-ii19.
[14] Evans, Laura, et al. "Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021." Critical care medicine 49.11 (2021): e1063-e1143.
[15] Timing and duration of surgical prophylaxis. Surg. NAPS (2020).
[16] European Centre for Disease Prevention and Control. Point prevalence survey of healthcare- associated infections and antimicrobial use in European acute care hospitals, 2016-2017. Stockholm: ECDC; 2023.

De-escalation

Antibiotic de-escalation is defined in the literature as:

- The transition from broad-spectrum antibiotics to a narrower spectrum or one with a lower ecological impact [17];
- The discontinuation of one or more components of an empirical combination therapy by suspending a molecule used in combination to ensure dual coverage against specific pathogens or discontinuing a molecule active against pathogens not isolated in cultures [18].

De-escalation should be performed as early as possible, at least within 24 hours of definitive culture results and antibiogram availability[19]. Its purpose is to reduce exposure to broad-spectrum antibiotics, thus diminishing their ecological impact and the emergence of resistance without negatively impacting patients. Even in neutropenic patients, there is no association between de-escalation and worsened patient outcomes.

De-escalation can be carried out independently of the infection site in the presence of microbiologically documented infection. However, in the case of complicated abdominal infections, anti-anaerobic coverage should be maintained because anaerobic microorganisms could be underdiagnosed due to the lower yield of cultures.

To help clinicians in selecting antibiotics with lower impact, the WHO has divided existing antibiotics into three categories: the ones with the lowest impact (ACCESS), the ones with a relevant impact whose use should be monitored (WATCH), and last resort antimicrobials that should be used only for multi-drug resistant phenotypes (RESERVE) (See Figure 1).

[17] De Waele, J. J., Schouten, J., Beovic, B., Tabah, A. & Leone, M. Antimicrobial de-escalation as part of antimicrobial stewardship in intensive care: no simple answers to simple questions—a viewpoint of experts. Intensive Care Med. 46, 236–244 (2020).

[18] Umpleby, H., Dushianthan, A., Catton, T. & Saeed, K. Antimicrobial stewardship programmes focused on de-escalation: a narrative review of efficacy and risks. J. Emerg. Crit. Care Med. 6, (2022).

[19] Tabah, A. et al. Antimicrobial de-escalation in critically ill patients: a position statement from a task force of the European Society of Intensive Care Medicine (ESICM) and European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Critically Ill Patient. Intensive Care Med. 46, 245–265 (2020).

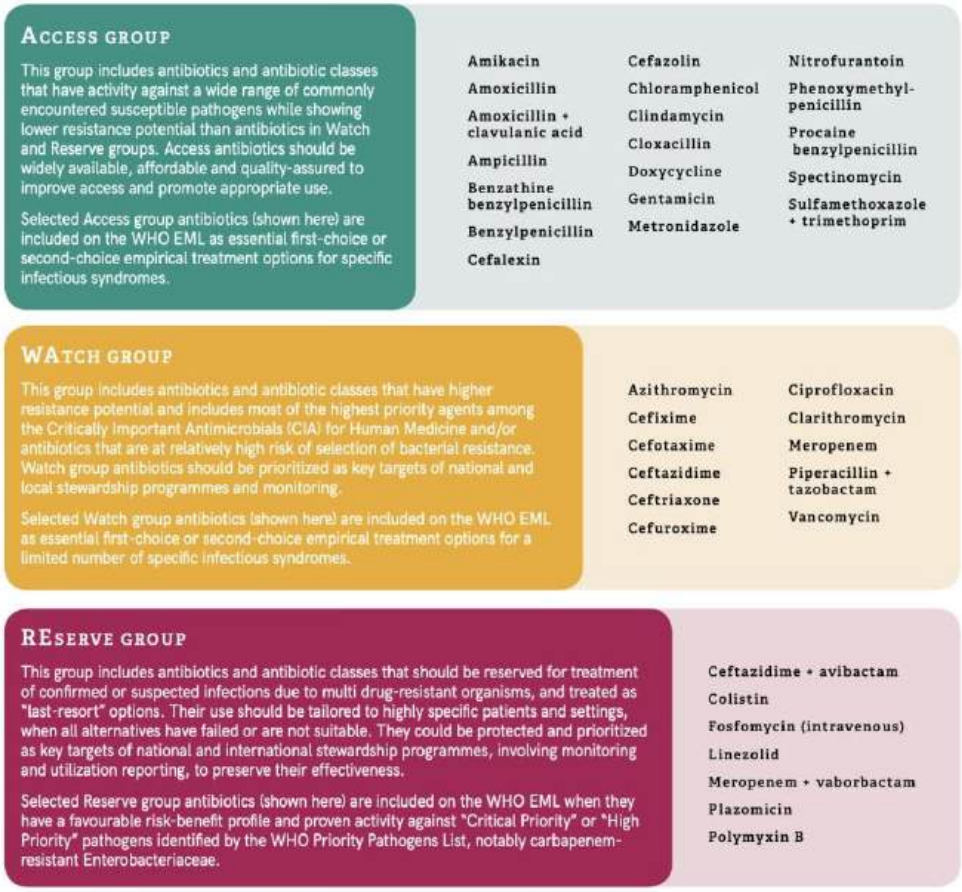

Figure 1: the WHO AWaRe classification[20]

Since β-lactams are often the first choice for empirical treatment, a more detailed definition of "appropriate spectrum" for this specific antibiotic class is offered to help audit and feedback assessment:

- **Appropriate:** the narrowest spectrum covering the isolate.
- **Prescription of excessive spectrum β-lactams (inappropriate):** prescription of a drug with excessive spectrum compared to *in vitro* results. The spectrum of β-lactams antibiotics is defined from broad to narrow following this ranking:
  - Active against carbapenemase-producers (some also eventually against CarbapenemResistant (CR) A. *baumannii, CR P. aeruginosa*): cefiderocol, ceftazidime/avibactam, meropenem/vaborbactam, imipenem/relebactam
  - Active against ESBL, AmpC (some* might eventually be active against some carbapenemaseproducers): imipenem*, meropenem*, cefepime/enmetazobactam*, ceftolozane/tazobactam.
  - Antipseudomonals: piperacillin/tazobactam, ceftazidime, cefepime, aztreonam
  - Active against ESBL and some AmpC, not antipseudomonal: ertapenem, temocillin

[20] World Health Organization. (2019). Antimicrobial stewardship programmes in health-care facilities in low- and middle-income countries: a WHO practical toolkit. World Health Organization. https://iris.who.int/handle/10665/329404. License: CC BY-NC-SA 3.0 IGO

- Cefotaxime, ceftriaxone
- Amoxicillin-clavulanic acid
- Amoxicillin, ampicillin

➢ **Prescription of not-needed combination therapy (inappropriate)** is defined as use of antigrampositive drugs (vancomycin, daptomycin, linezolid, etc.) in infections caused by gram-negative bacteria or *vice versa*, use of a non-active antigram-negative drug according to in vitro result, or a redundant drug (because of other active drugs) in patients without a justified reason for combination therapy according to ESCMID guidelines for treatment of MDR gram negatives.

➢ **Prescription of too narrow spectrum β-lactams (inappropriate)** need of a drug with a broader spectrum (according to the antibiotic ranking displayed above).

➢ **Lack of combination therapy (inappropriate):** Adding another drug to a monotherapy/combination is necessary to treat the isolate adequately.

Switch to oral

Switching to oral therapy allows for earlier hospital discharge, reducing the risk of new infectious episodes, especially catheter-related infections. Additionally, it helps lower hospital costs and improves the patient's quality of life. [21]

The rationale for starting with intravenous therapy in severe infections is linked to the possibility of rapidly achieving effective concentrations. However, increasing evidence suggests that, after the initial 48-72 hours of intravenous treatment, a switch to oral therapy should be considered in patients with a good clinical response and adequate intestinal absorption. This recommendation is supported by the "National Institute for Health and Care Excellence AMS guidelines" and the "UK Health Security Agency" [22].

The latter has also provided guidance for assessing the possibility of an oral switch, particularly considering the following elements:

- clinical improvement: body temperature between 36 and 38°C in the previous 24 hours, reduction in the Early Warning Score, a decreasing trend in white blood cells and protein C reactive,
- patient's ability to take oral therapy or enteral administration in the absence of intestinal malabsorption,
- drug bioavailability, absence of pharmacological interactions or allergies,
- no issues with adherence to oral treatment or episodes of vomiting in the last 24 hours.

[21] UK Health Security Agency. Antimicrobial Intravenous-to-Oral Switch (IVOS) Decision Aid Based on the National Antimicrobial IVOS Criteria. 55, 2023 (2023).

Antimicrobial stewardship in Australian health care. JAC-Antimicrobial Resistance 1, (2019).

[22] McCarthy, K. & Avent, M. Oral or intravenous antibiotics? Aust. Prescr. 43, 45–48 (2020).

Landersdorfer, C. B., Gwee, A. & Nation, R. L. Clinical pharmacological considerations in an early intravenous to oral antibiotic switch: are barriers real or simply perceived? Clin. Microbiol. Infect. 29, 1120–1125 (2023).

Knowing the pathogen responsible for the infection is essential for setting up an oral therapy as appropriate as possible. In choosing the molecule, it is necessary to consider its spectrum of action, bioavailability, penetration into the affected site, and potential side effects.

Available oral antibiotics can be categorized as follows according to their bioavailability:

- 90%: levofloxacin, clindamycin, metronidazole, doxycycline, rifampin, linezolid.
- 80-90% amoxicillin, cefadroxil, cephalexin, ciprofloxacin, moxifloxacin, and cotrimoxazole.
- 60-70% penicillin VK.
- < 60% dicloxacillin, cefuroxime, cefixime, cefpodoxime, cefdinir, amoxicillin-clavulanate, azithromycin, fosfomycin, clarithromycin.

Finally, special attention is given to certain specific conditions where the switch to oral antibiotic therapy requires specialist evaluation and increased attention. These conditions include deep-seated infections, infections requiring high antibiotic concentrations or traditionally treated with prolonged intravenous therapy, and critical clinical conditions with a high risk of mortality. Infections that necessitate specialist evaluation and adherence to specific guidelines are bloodstream infections, endocarditis, empyema, meningitis, osteomyelitis, severe or necrotizing soft tissue infections, septic arthritis, and abscesses without source control.

Duration

The overall duration of the antibiotic therapy should be in line with guidelines and should be discontinued if there is no clinical evidence of infection. Broad-spectrum empirical treatment should be modified to targeted therapy as soon as the results of cultures are available. A review of the therapy should be conducted after the first 72 hours or as soon as microbiological results are available[23]. More than 120 randomized clinical trials have established that short-course antimicrobial regimens are as effective as prolonged ones with a lower risk of side effects. Longer regimens exert selective pressure on the environment, promoting the emergence of antibiotic resistance. Similarly, they are associated with a higher risk of adverse reactions and the development of invasive fungal infections or CDIs[24].

However, some specific types of infections deviate from the "shorter is better" concept, and reducing the duration of therapy may not be equally effective. Such infections include prosthetic infections with device retention, chronic pulmonary aspergillosis, and otitis media in children under two years old.

In immunocompromised patients, excessively prolonged antibiotic therapy is associated with the same risks as the general population, albeit with a higher frequency, and is also linked to higher mortality. However, there is limited data regarding the short duration of antibiotic therapy in this population, and further studies are necessary[25].

[23] Monnier, A. A. et al. Quality indicators for responsible antibiotic use in the inpatient setting: A systematic review followed by an international multidisciplinary consensus procedure. J. Antimicrob. Chemother. 73, vi30–vi39 (2018).

[24] Lee, R. A., Stripling, J. T., Spellberg, B. & Centor, R. M. Short-course antibiotics for common infections: what do we know and where do we go from here? Clin. Microbiol. Infect. 29, 150–159 (2023).

Davar, K. et al. Can the Future of ID Escape the Inertial Dogma of Its Past? The Exemplars of Shorter Is Better and Oral Is the New IV. Open Forum Infect. Dis. 10, 1–9 (2023).

[25] Imlay, H., Laundy, N. C., Forrest, G. N. & Slavin, M. A. Shorter antibiotic courses in the immunocompromised: the impossible dream? Clin. Microbiol. Infect. 29, 143–149 (2023).

The following table reports results from RCTs that compared shorter to longer duration in various clinical syndromes. [26]

Population/Syndrome	RCT/Systematic Review	Shorter Duration	Longer Duration	Outcomes
Pneumonia	Capellier 2012	8 days	15 days	No difference
	Chastre 2003	8 days	15 days	No difference
	El Moussaoui 2006	3 days	8 days	No difference
	Fekih Hassen 2009	7 days	10 days	No difference
	File 2007	5 days	7 days	No difference
	Kollef 2012	7 days	10 days	No difference
	Leophonte 2002	5 days	10 days	No difference
	Medina 2007	8 days	12 days	No difference
	Siegel 1999	7 days	10 days	No difference
	Tellier 2004	5 days	7 days	No difference
Bacteremia	Chaudhry 2000	5 days	10 days	No difference
	Runyon 1991	5 days	10 days	No difference
	Yahav 2018	7 days	14 days	No difference
	Molina 2022	7 days	14 days	No difference
Intra-abdominal infection	Montravers 2018	8 days	15 days	No difference
	Sawyer 2015	Max. 5 days	Max. 10 days	No difference
Urinary tract infection	Peterson 2008	5 days	10 days	No difference

Appropriateness of culture

In the suspicion of a bacterial infection, it is necessary to collect appropriate microbiological samples based on the possible site of infection before initiating antibiotic therapy. This allows for the adjustment, or initiation, of the most appropriate and narrow-spectrum therapy based on the microbiological outcome.[27]

Diagnostic stewardship can be divided into three phases: pre-analytical, analytical, and postanalytical[28].

In the pre-analytical phase, the most appropriate microbiological test should be selected based on signs and symptoms, avoiding tests that may be associated with low diagnostic yield or a high rate of false positives. This ensures accurate antibiotic selection based on relevant results.

[26] Evans, L; Rhodes, A et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. Critical Care Medicine 49(11):p e1063-e1143, November 2021. | DOI: 10.1097/CCM.0000000000005337

[27] Monnier, A. A. et al. Quality indicators for responsible antibiotic use in the inpatient setting: A systematic review followed by an international multidisciplinary consensus procedure. J. Antimicrob. Chemother. 73, vi30–vi39 (2018).

[28] Antimicrobial stewardship in Australian health care. JAC-Antimicrobial Resistance 1, (2019).

In the analytical phase, the laboratory plays a crucial role in reducing unnecessary tests, for example, by rejecting samples under specific conditions (such as conducting *C. difficile* testing without diarrheal stools).

The post-analytical phase relies on the correct interpretation of results. Results must be provided quickly to reduce the duration of empirical therapy and enable the prompt initiation of the most appropriate treatment[29].

Blood-cultures

Blood cultures represent the cornerstone of culture tests. A recent literature review suggests their performance in clinical syndromes with a high pre-test probability of bacteremia, such as septic shock, meningitis, endovascular infections, osteomyelitis, epidural abscesses, and non-traumatic septic arthritis. It also suggests considering their use when it is not possible to collect cultures directly from the site of infection or when starting antibiotic therapy before sampling. This is the case in patients with complicated UTIs recently treated with antibiotics at home or unable to undergo a urine culture or in acute obstructive cholangitis, where therapy is initiated before endoscopic procedures.

Finally, it is advised not to perform blood cultures in specific conditions due to the low incidence of bacteremia or because the microbiological outcome does not provide additional relevant information or has no clinical impact. This applies to febrile episodes within 48 hours of surgery, non-severe community-acquired pneumonia, hospital-acquired pneumonia, cystitis, and prostatitis[30].

Urine culture

Urine culture collection plays a pivotal role in diagnosing and managing urinary tract infections (UTIs), providing valuable insights into the presence of bacteria in the urinary system. However, incorrect urine culture collection in patients without symptoms is one of the highest drivers of antimicrobial overuse. Asymptomatic bacteriuria refers to the presence of bacteria in the urine without any accompanying symptoms of infection. This phenomenon is common, particularly among certain demographic groups such as elderly individuals with indwelling urine catheters, and it has been identified as an essential target for ABS interventions. Diagnostic stewardship is based on the principle that a positive culture—even in an asymptomatic patient—is a powerful stimulus for treatment and leads to unnecessary prescriptions. Despite several guidelines recommending against treating asymptomatic bacteriuria in most hospitalized patients, up to 80% are treated with antibiotics.[31,32] To combat this antibiotic overuse, diagnostic stewardship (avoiding unnecessary urine cultures) and antibiotic stewardship (avoiding or stopping unnecessary antibiotic use in asymptomatic patients found to have a positive urine culture) need to be proposed as potential ABS targets.

[29] Zakhour, J. et al. Diagnostic stewardship in infectious diseases: a continuum of antimicrobial stewardship in the fight against antimicrobial resistance. Int. J. Antimicrob. Agents 62, 106816 (2023).

[30] Fabre, V. et al. Does this patient need blood cultures? A scoping review of indications for blood cultures in adult nonneutropenic inpatients. Clin. Infect. Dis. 71, 1339–1347 (2020).

[31] Nicolle LE, Gupta K, Bradley SF, et al. Clinical practice guideline for the management of asymptomatic bacteriuria: 2019 update by the Infectious Diseases Society of America. Clin Infect Dis. 2019;68(10):e83-e110. doi:10.1093/cid/ciz021

[32] Sloane PD, Kistler CE, Reed D, Weber DJ, Ward K, Zimmerman S. Urine culture testing in community nursing homes: gateway to antibiotic overprescribing. Infect Control Hosp Epidemiol. 2017;38(5):524-531. doi:10.1017/ice.2016.326

Dose and intervals

The antibiotic dose and administration frequency should adhere to the guidelines. Suboptimal doses contribute to inadequate antibiotic treatment, making it less effective against the pathogen causing the infection, leading to an increased mortality rate. The dosage and administration frequency should be adjusted in cases of renal and hepatic insufficiency to reduce the risk of developing drug-related side effects or toxicity. On the other hand, in critically ill patients with abnormal renal filtration, the antibiotic dose might be suboptimal, resulting in an increased risk of mortality. Various factors in these patients can make it challenging to maintain adequate antibiotic levels, such as the need for continuous renal replacement therapy or, conversely, an augmented renal clearance with rapid drug elimination, the specific characteristics of the antibiotic, physio pathological alterations like hypoalbuminemia and an increased volume of distribution leading to quick drug elimination, the minimum inhibitory concentration (MIC) of the responsible pathogen, and finally, the site of infection, which could be more challenging to reach at times requiring an increased dose for some antibiotics.

Therapeutic drug monitoring is crucial in accurately assessing antibiotic exposure in these contexts.[33]

Antibiotic plan

The antibiotic plan specifies in the medical documentation the rationale for initiating antibiotic therapy before its start, especially when deviating from guidelines. It should include details such as the name of the antibiotic, the dosage and administration interval, the treatment duration, and the administration route. Details should accompany this information on clinical and laboratory parameters indicative of sepsis, and similarly, microbiological results should be reported[34].

Early stop or no start

The antibiotic therapy should be discontinued without clinical evidence of infection. The presence of negative cultures does not allow the exclusion of an infection. Negative cultures may result from either a non-infectious clinical condition mimicking sepsis or exposure to prior antibiotic therapies, inadequate collection techniques, or slow-growing microorganisms. The non-infectious clinical condition must be distinguished from culture-negative sepsis, as it is associated with mortality rates comparable to culture-positive sepsis. Conversely, antibiotic treatment for a non-infectious condition exposes the patient to the adverse effects of therapy without reaping its benefits[35].

Finally, a recent literature review has suggested that, for specific patients admitted to the intensive care unit (ICU) who are constantly and closely monitored, in the absence of immediately lifethreatening infections, the advantages of early empirical antibiotic therapy versus delayed targeted

[33] Gatti, M. & Pea, F. Antimicrobial Dose Reduction in Continuous Renal Replacement Therapy: Myth or Real Need? A Practical Approach for Guiding Dose Optimization of Novel Antibiotics. Clin. Pharmacokinet. 60, 1271–1289 (2021).

Fiore, M., Peluso, L., Taccone, F. S. & Hites, M. The impact of continuous renal replacement therapy on antibiotic pharmacokinetics in critically ill patients. Expert Opin. Drug Metab. Toxicol. 17, 543–554 (2021).

[34] Monnier, A. A. et al. Quality indicators for responsible antibiotic use in the inpatient setting: A systematic review followed by an international multidisciplinary consensus procedure. J. Antimicrob. Chemother. 73, vi30–vi39 (2018).

Antimicrobial stewardship in Australian health care. JAC-Antimicrobial Resistance 1, (2019).

[35] Kadri, S. S. et al. Early Discontinuation of Antibiotics in Patients Admitted With Clinically Suspected Serious Infection but Negative Cultures: Retrospective Cohort Study of Practice Patterns and Outcomes at 111â US Hospitals. Open Forum Infect. Dis. 10, 1–10 (2023).

antibiotic therapy are minimal if the targeted therapy is appropriate in terms of indication and dosage and is accompanied by adequate source control[36].

2.2 ABS Strategy

2.2.1 Engaging key figures

The REVERSE ABS implementation relies on the collaborative efforts of a local multidisciplinary team that engages with prescribers in the REVERSE wards to promote ABS interventions. As a minimum standard, the team should include at least a clinician with expertise in antibiotic therapy (Infectious diseases physician or other prescribers) and a pharmacist. Periodic meetings with the Microbiology and the IPC departments should also be established to share common goals and strategies. As additional support, the Information Technology department could contribute to systematizing the flow of relevant data (antibiotic use and microbiology data) and automatize reporting activities.

Formal recognition of the team by the hospital direction and a written program that identifies roles and responsibilities are vital steps for ensuring a successful implementation. Ideally, team members should have protected time to engage in ABS activities.

Prescribers from participating wards are the primary target of ABS activities. Therefore, they should be directly involved in the implementation process. The selection of ward champions can facilitate communication between the wards and the ABS team and foster a more successful collaboration. Among non-prescribers, nurses might be valuable assets for improving critical aspects of antibiotic prescribing by improving adherence to diagnostics and therapeutic protocols.

For the ABS program within REVERSE, all participating hospitals must identify at least two prescribers to be engaged in ABS activities as 'ward champions'. The ward champions will support the ABS team with the ABS activities (e.g., implementation of guidelines, access to antibiotic prescriptions, provision of feedback to all prescribers within the ward). An official recognition by the hospital leadership will be sought to identify roles and responsibilities formally. Official reports on antibiotic use and guidelines adherence will be drafted during the ABS program to provide feedback to the participating wards.

2.2.2. Planning the REVERSE ABS Implementation

It is often common understanding that ABS especially concerns patients with severe and difficult-totreat infections for whom the right antibiotic at the right time and dose can be lifesaving. However, it must be underlined that those patients are only a minority of those receiving antibiotics during their hospitalization. Even though it cannot be argued that the contribution of Infectious Diseases specialists, microbiologists, and pharmacists is crucial for such therapeutic optimizations, it is important to underline that, to have a real impact, ABS should concern a higher quantity of patients and cannot rely only on ID consultations.

To better express this concept and to help ABS teams plan their ABS interventions, we represented the REVERSE ABS strategy as a fruit tree with high-risk areas (hemato-oncology and ICU) depicted as high-

[36] Denny, K. J., De Wale, J., Laupland, K. B., Harris, P. N. A. & Lipman, J. When not to start antibiotics: avoiding antibiotic overuse in the intensive care unit. Clin. Microbiol. Infect. 26, 35–40 (2020).

hanging fruits. The ABS' ladder' will help the teams to harvest the ABS fruit starting from targets that involve 'easier' prescriptions and a substantial number of patients (i.e., surgical prophylaxis and appropriateness of urine culture). Hospitals with more resources (e.g., electronic prescription) or building on already existing ABS interventions can progress further and target other antibiotic prescriptions.

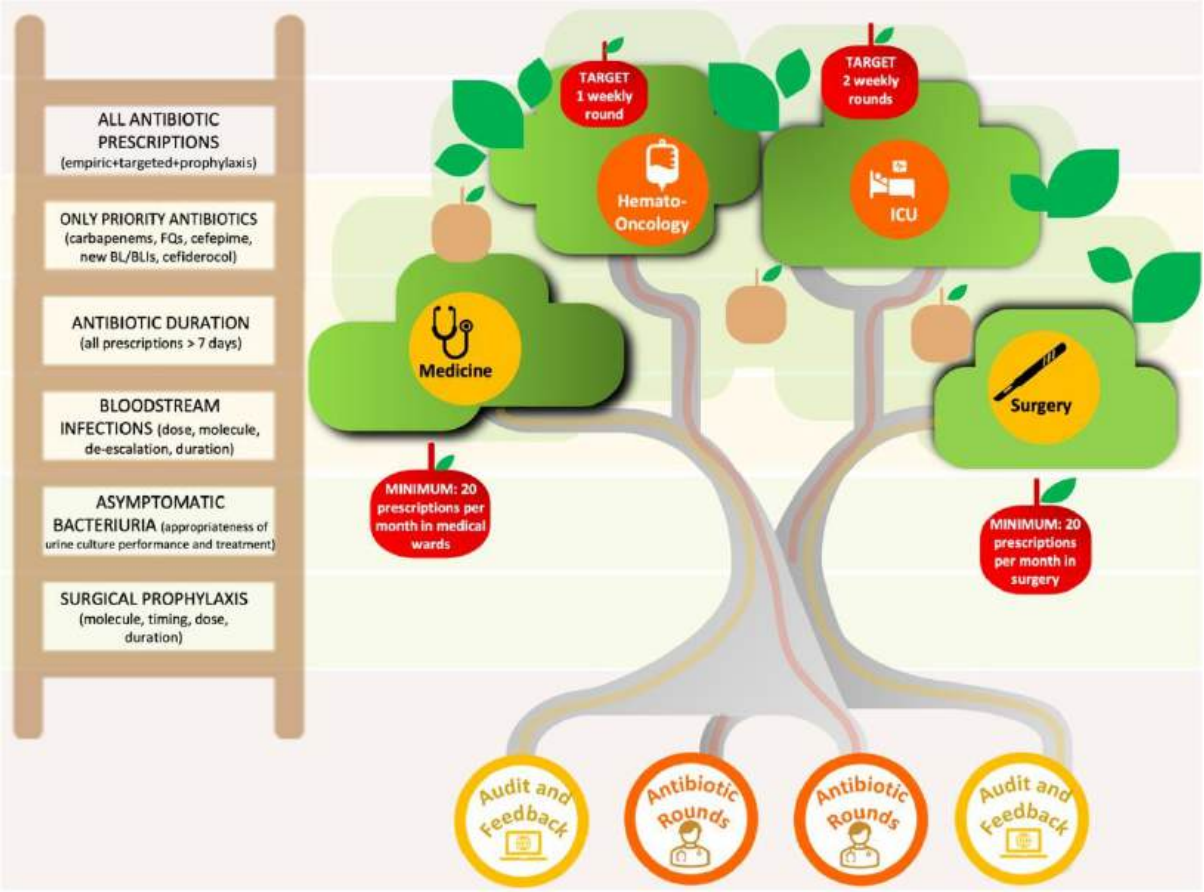

Figure 2 The REVERSE ABS tree

2.2.3 Overall strategy and development

As per the REVERSE plan, the kick-off of the ABS implementation activities will be preceded by an onsite workshop targeting the representatives of the local ABS team identified by each REVERSE hospital. During the workshop, the overall ABS strategy will be presented with a specific focus on how to plan an effective implementation. Practical tools and examples on how to plan the intervention and how to perform audit and feedback will be offered to the local ABS team. Additional educational events might also target specific hospitals or specialties according to the needs emerging during the implementation phase.

The basic best practice intervention of the ABS module will include the following elements:

- Guidelines provision

The WP4 will collaborate with each national focal point to revise local protocols and assess any need for updates/modification/integration with local ABS teams. For the hospitals where no local guidelines are available, therapeutic indications for the most common infectious disease syndrome treated at the hospital level will be provided based on the most recent international recommendations (namely, empiric therapy, surgical prophylaxis, recommendations on duration and de-escalation, indications on the use of novel antibiotics for treating CR-GNB infections) and considering their local epidemiology (when possible). The indications will be provided to the prescribers of the target wards and will serve as a reference for the audit and feedback activities (annex 4.1).

- ***Assessment of appropriateness of antibiotic prescriptions through cross-sectional Audit and Feedback in the medical and surgical area***

Starting from the first month after the Workshop (M1 of the ABS intervention), antibiotic auditing will be performed by a member of the local ABS team through a periodic evaluation of the antibiotic prescriptions in the target wards. The professional performing audit and feedback activities will need to be part of the ABS team and work outside the target ward to avoid bias in evaluating prescription appropriateness. An electronic module via RedCap (annex 4.2) adapted from existing surveys (i.e., ECDC and Australian NAPS) will be made available to the local ABS team to homogenize the process, facilitate feedback, and allow a standardized data collection.[37] Only aggregate performances on the appropriateness of antibiotic use and periodic point prevalence of patients receiving antibiotics will be collected centrally. No patient-level identifiers will be collected centrally, and only very limited clinical variables (i.e., age, sex, allergies, admission date, and suspected diagnosis) will be recorded for the appropriateness evaluation. Pseudo-anonymized data (i.e., patients' code) will be recorded locally only for feedback provision. Feedback will be provided by the local ABS team to the ward prescribers in a timely manner (maximum after 24-48 hours from the data collection) so that suggestions on improving prescriptions can be reflected in immediate patient care. The modality of feedback provision will be agreed locally with the ward champions of each REVERSE ward.

All participating hospitals will identify prescriptions they would like to focus their efforts on. As a minimum requirement for all hospitals, covering at least **one basic target in the medical area (e.g., treatment of asymptomatic bacteriuria) and one basic target in the surgical area (e.g., surgical prophylaxis) is recommended.** Additional targets might be included according to the ABS team's preferences and the feasibility in terms of the prescriptions' data flow. For example, audit and feedback of 'all the prescriptions' can be complex if prescriptions are not electronic. Easier targets might be 'de-escalation for microbiologically documented bloodstream infections' or 'indication for broad-spectrum antibiotics' since they would require only microbiology or pharmacy data access.

If electronic prescriptions are in place, evaluation of treatments longer than 7 days may also be a target. Additionally, since REVERSE is targeting infections sustained by MDR-Gram-negatives, some specific antibiotic molecules could be prioritized for audit and feedback activities (e.g., carbapenems, fluoroquinolones, piperacillin/tazobactam, cefepime, newer antibiotics with anti-CRE activity). In

[37] James R, Nakamachi Y, Morris A, So M, Ponnampalavanar SSS, Chuki P, Loong LS, Lai PSM, Chen C, Ingram R, Rajkhowa A, Buising K, Thursky K. The feasibility and generalizability of assessing the appropriateness of antimicrobial prescribing in hospitals: a review of the Australian National Antimicrobial Prescribing Survey. JAC Antimicrob Resist. 2022 Feb 9;4(1):dlac012. doi: 10.1093/jacamr/dlac012. PMID: 35156035; PMCID: PMC8827555.

European Centre for Disease Prevention and Control. Protocol for point prevalence surveys of healthcare-associated infections and antimicrobial use in European long-term care facilities – version 4.0. Stockholm: ECDC; 2023.

hospitals where prescriptions are not electronic or easily accessed by the ABS local team, the ward champions might help provide the ABS team with a periodic list of patients receiving antibiotics. Details and definitions to be applied during the process are summarized in the table below.

AUDIT DEFINITIONS	
Audit type: The audit process can be either cross-sectional (i.e., the evaluation of the appropriateness of the antibiotic prescription at a specific time point) or longitudinal (i.e., the assessment of part of the course /the entire course of one particular antibiotic).	
Audit timeframe: The team also needs to select the period for which the appropriateness of prescriptions will be evaluated. The chosen timeframe must allow for the evaluation of a meaningful number of prescriptions (e.g., all patients receiving antibiotics on a given day for cross-sectional audits, all 'priority antibiotics' prescribed in a week/month, all positive blood cultures in a month...).	
Target prescriptions: The group of prescriptions that are evaluated during an audit session (see below)	
TARGET PRESCRIPTIONS	
All prescriptions (cross-sectional)	
Definition	All systemic antibiotics prescribed on a given day (generally, the same day of the audit starting from 8.00 AM).
Prescription type	All prescriptions - *Surgical prophylaxis*: any antibiotic administered to a non-infected surgical patient to prevent surgical site infections (SSIs). - *Medical prophylaxis*: any antibiotic administered with the aim of preventing opportunistic infections. - *Empiric therapy*: any antibiotic administered pending culture results or when culture is negative or not performed. - *Target therapy*: any antibiotic administered after 24-48 hours from receiving definitive microbiological results.
Data flow	Electronic prescriptions Manual (reported by the ward champions or collected by the ABS team from paper charts)
Only 'priority antibiotics' (longitudinal)	
Definition	All antibiotics are considered a priority according to local practice. Suggested priorities within REVERSE are carbapenems, fluoroquinolones, piperacillin/tazobactam, cefepime, new BL/BLIs
Prescription type	All prescriptions of 'priority antibiotics' (can be used as prophylaxis or treatment, in the case of treatment, can be empiric, targeted, or both).
Data flow	Electronic prescriptions, pharmacy database of restricted antibiotics, manual (reported by the ward champions or collected by the ABS team from paper charts)
Microbiologically documented infections (longitudinal)	

Definition	All systemic antibiotics that are prescribed to treat suspected BSIs and UTIs. Patients' selection starts from microbiological samples: - Only microbiologically documented BSIs in a pre-defined time period-> Evaluate the empiric and the targeted therapy administered for the index blood culture (include only the first clinically significant isolate per each patient; coagulase-negative Staphylococci can be excluded). - Only microbiologically documented UTIs or asymptomatic bacteriuria in a pre-defined period -> Evaluate the empiric (if any) and the targeted therapy (if any) for the index urine culture with any bacterial load (list 'no antibiotic' if the microbiological results were deemed as non-significant, also polymicrobial urine cultures can be considered to optimize the management of asymptomatic bacteriuria).
Prescription type	Any antibiotic that has been used to treat the suspected UTI or BSI (starting from the time of the culture collection to the time of the stop of the targeted treatment if the sample was deemed significant).
Data flow	Microbiology database and patients' charts
Surgical prophylaxis (cross-sectional OR longitudinal)	
Definition	All antibiotics are administered peri-operatively to prevent surgical site infections
Prescription type	Any antibiotic administered to a non-infected patient who has undergone surgery in the pre-defined timeframe (single day, week, month). If cross-sectional: all patients receiving surgical prophylaxis that given day (irrespective of the time of the surgery; ideally, the whole surgical ward should be included). If longitudinal: all patients who underwent surgery during the pre-defined timeframe should be included (the whole prophylaxis should be evaluated in terms of indication, timing, doses, and duration).
Data flow	Electronic prescriptions, operating room register, manual
Antibiotic duration (longitudinal)	
Definition	All the antibiotics lasting more than a given timeframe (e.g., 72 hours, 7 days)
Prescription type	Any antibiotic that is administered longer than a given timeframe. The suggested timeframe is 72 hours to prompt the re-evaluation of empiric treatment by clinicians and 7 days to encourage adherence to treatment guidelines in terms of duration. The evaluation is longitudinal, and the given antibiotic can be used with all possible indications (prophylaxis or therapeutic, empiric or targeted, or both).
Data flow	Electronic prescriptions, pharmacy database, manual.
DEFINITION OF APPROPRIATENESS	
Appropriate	The therapy follows local guidelines regarding antibiotic choice, dose, route, and duration OR treatment that will cover the (likely) causative pathogen, and there is no narrower spectrum or more appropriate antibiotic available, OR therapy follows the indication of the 'antibiotic expert' consultant.
Adequate	Therapy is not the optimal choice, but it is a reasonable alternative to cover the (likely) causative agent regarding antibiotic choice, dosage, route, or duration.

Inappropriate	Therapy is an unreasonable choice to cover the (likely) causative pathogen (in terms of molecule or dosage or route or duration), including: ■ excessive spectrum (i.e., a 'Watch' antibiotic when an 'Access' antibiotic is recommended in the guidelines or reported as susceptible in the antibiogram) ■ antibiotic is added as an unnecessary combination. ■ The dosage is inadequately low or high / the duration is too long. ■ There is a significant mismatch with the recommended route of administration (i.e., an antibiotic with poor oral bioavailability prescribed per os for a severe infection, intravenous vancomycin for C. diff….). ■ There is a significant allergy mismatch (the patient is allergic to the prescribed antibiotic OR there are more appropriate alternatives for the patient's allergy).
Not assessable	The indication was not documented and cannot be determined from the notes.

Regardless of the status of the existing ABS activities, all hospitals will be asked to fill in the dedicated REVERSE tool for **at least** two rounds of audit and feedback per month with a minimum of 20 prescriptions in the medical and 20 prescriptions in the surgical area with no restriction on the target prescription evaluated (i.e., at least asymptomatic bacteriuria and surgical prophylaxis). Additional audits and feedback (in terms of audit type and frequency) could be performed according to the ABS team resources. A one-year audit and feedback activities are foreseen for each hospital starting from April 2024 for the first cohort of hospitals.

- Revision of prescriptions through antibiotic rounds in high-risk wards

Hospitals with advanced ABS programs are encouraged to choose among the 'higher hanging fruits', such as the systematic revision of prescriptions in onco-hematology and ICU areas.

Thus, the ABS team could approach the wards through 'antibiotic rounds' to be carried out once or twice a week to review and discuss all antibiotic prescriptions with the ward doctors. The prevalence of patients receiving antibiotics will be recorded weekly, and periodic feedback based on case discussion will be performed with all the prescribers to focus on stewardship goals and provide feedback on the activities.

Other wards might also be selected for a more systematic revision of antibiotic prescription, especially those with higher MDR prevalence or antibiotic consumption. Selection of the wards will be based on local resources and on data collected during the first 18 months of the study on AMR rates and antibiotic consumption.

- Monitoring of antimicrobial consumption

Antibiotic consumption is recorded within the REVERSE clinical study starting from month 1. Overall and single-class consumption feedback will be monitored during the intervention and every six months until the end of the study. Where available, ward-level consumption and aggregate data following the WHO-AWaRe classification will be collected and, if feasible locally, reported following existing recommendations.[38] Since REVERSE is targeting infections sustained by MDR-Gram Negatives, the

[38] Pezzani MD, Carrara E, Sibani M, Presterl E, Gastmeier P, Renk H, Kanj SS, Velavan TP, Song LH, Leibovici L, Torumkuney D, Kostyanev T, Mendelson M, Tacconelli E; ARCH working group. White Paper: Bridging the gap between human and animal surveillance data, antibiotic policy and stewardship in the hospital sector-practical guidance from the JPIAMR ARCH and COMBACTE-MAGNET EPI-Net networks. J Antimicrob Chemother. 2020 Dec 6;75(Suppl 2):ii20-ii32. doi: 10.1093/jac/dkaa426. PMID: 33280046; PMCID: PMC7719407.

following antibiotic molecules are considered a priority and will be subjected to specific monitoring: **carbapenems, piperacillin/tazobactam, cefepime, fluoroquinolones, new antibiotics with activity against CRE.**

2.2.4 Risks & Benefits

This study will comply with the protocol approved by the Institutional Review Board and according to Good Clinical Practice standards. No separate IRB approval will be requested for the basic WP4, as all data collected were part of the IRB submission for the clinical study.

The ABS program represents a quality improvement project based on educational and 'enabling' elements and does not include any 'restrictive' interventions. We expect patients admitted to the study-wards will receive more appropriate therapies and, overall, a reduced amount of unnecessary antibiotics. The risks related to this study are minimal. Potential risks to all patients admitted into the participating wards include the loss of confidentiality of individual health information collected as part of the study; however, these risks will be rare since only de-identified patient-level information will be collected. Access to study records will be restricted to study staff and investigators. Every effort will be made to keep the study records as confidential as possible using assignments of unique participant identifiers, password-protected databases, and storage of paper records in locked filing cabinets in locked rooms when not in use.

The ABS team's suggestions and recommendations over the quality of prescriptions could potentially create a 'negative professional culture', especially in wards where the prescribers are not sufficiently engaged with the project or there is no 'readiness' towards the change. This and other topics relative to implementation science will be covered by WP5 during the preliminary workshop so that every ABS team has the necessary knowledge to analyze and strategically tackle those situations.

3. Outcomes and process indicators

WP4 outcomes and process indicators are summarized in the table below.

<table>
<tr><td>TIMELINE</td><td>MONTH 30 (Dec 2023) -> MONTH 57 (Mar 2026).
The implementation of the ABS activities follows the stepped-wedge design of the Master Protocol.
<table>
<tr><th>Cohort</th><th>Preparatory phase start</th><th>ABS intervention Start</th><th>ABS intervention End</th></tr>
<tr><td>1</td><td>January 2024</td><td>April 2024</td><td>April 2025</td></tr>
<tr><td>2</td><td>April 2024</td><td>July 2024</td><td>July 2025</td></tr>
<tr><td>3</td><td>July 2024</td><td>October 2024</td><td>October 2025</td></tr>
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</td></tr>
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	4	October 2024	January 2025	January 2026
PARTICIPANTS	ALL HOSPITALS (by cohort)			
LEAD PARTNER	UNIVR and SAS; Other partners involved: NKUA, UMFCD, WP2, WP5			
ACTIONS	**Preliminary** ➢ Identify ABS teams and training (ABS survey, meetings, and workshop). ➢ Identification of reference documents (local or national) on judicious antibiotic use. ➢ Measure antibiotic consumption (ideally from March 2022, to be carried out until March 2026, minimum March 2023-March 2025). **Intervention (April 2024 for the first cohort until all 24 hospitals have adopted the intervention nine months later, January 2025.)** ➢ Periodic audits and immediate feedback to the unit (written and via antibiotic rounds) on compliance with guidance on antibiotic use (months 34-42). ➢ At least two monthly audits and feedback (one medical and one surgical ward) with a minimum of 40 prescriptions. ➢ Provide periodic reports on antimicrobial consumption and establish pathways for integrating antibiotic consumption reporting to inform antibiotic stewardship policies (should also be sustained after REVERSE, but at least months 34-42).			
EXPECTED TARGETS TO BE REACHED IN EVERY HOSPITAL AFTER THE BASIC INTERVENTION	**MINIMUM TARGETS** ➢ Establishment of an ABS team with dedicated time and clearly defined activities and roles. ➢ Provision of hospital guidelines reflecting ABS indications on empiric antibiotic use and treatment of MDR infections according to national policies. ➢ Establishment of audit activities, antibiotic rounds, and feedback on the appropriateness of prescriptions in selected wards.			
	➢ Establishment of ward champions among participating REVERSE wards. ➢ Creation of periodic reporting of hospital-wide data on HAI surveillance and AMU. **IDEAL TARGETS** ➢ The hospital administration officially acknowledges a written ABS program. ➢ The periodic report should provide data per hospital ward/area (i.e., internal medicine vs. surgery vs ICU vs haemato-oncology). ➢ Periodic data sharing and benchmarking of AMR and AMU data among similar wards in all the REVERSE hospitals (national or international). This could be implemented via a periodic report for each hospital area and periodic meetings of the same specialties between different hospitals. ➢ Provision of hospital guidelines reflecting ABS indications on empiric antibiotic use, surgical prophylaxis, and treatment of MDR infections tailored to local epidemiology.			

PROCESS INDICATORS TO BE MONITORED IN EVERY HOSPITAL DURING THE BASIC INTERVENTION TO CAPTURE THE INTERVENTION EFFICACY	**MINIMUM** Reduction of overall antibiotic consumption in the REVERSE wards measured as quarterly DDDs/PDs with an interrupted-time series model comparing the 12 months pre- to the 12 months post-intervention period. **IDEAL** Reduction of overall antibiotic consumption measured as above in specific REVERSE wards/areas. **MINIMUM** Reduction of consumption of priority antibiotic classes (i.e., carbapenems, piperacillin/tazobactam, cefepime, fluoroquinolones, new antibiotics with activity against CRE) in the REVERSE wards measured as quarterly DDDs/PDs with an interrupted-time series model comparing the 12 months pre- to the 12 months post-intervention period. **IDEAL** Reduction of consumption of priority antibiotic classes (measured as above in single REVERSE wards/areas. **MINIMUM** increase of the hospital-wide ACCESS: WATCH ratio (according to the WHO definition) comparing the pre- to the post-intervention period **IDEAL** increase of single wards/areas ACCESS: WATCH ratio (according to the WHO definition) comparing the pre- to the post-intervention period **MINIMUM** increase trend of the appropriateness of antibiotic prescriptions according to local guidelines (empiric therapy), and ASP principles (de-escalation, duration, combination…) to be assessed via periodic audits and feedback in the REVERSE wards.
OUTCOMES	Reduction of HAI caused by target MDR. Reduction of length of hospital stay (per ward/area). Reduction/stability of ward-aggregated mortality rates. Reduction/stability of ward-aggregated re-admission rates.

Table 2. Summary of the ABS basic intervention timeline, actions, and process indicators.

List of abbreviations

ABS	Antimicrobial stewardship
AFD	Antibiotic Free Days
AMR	Antimicrobial resistance
AMU	Antimicrobial use
AWaRe	Access, Watch and Reserve
CDI	Clostridium difficile infection
CRE	Carbapenem resistant Enterobacterales
DDD	Defined-Daily Dose
DOT	Day Of Therapy
ECDC	European Centre for Disease Prevention and Control
ESBL	Extended-spectrum beta-lactamase
HAI	Hospital-acquired infection
ICU	Intensive Care Unit
IDSA	Infectious Diseases Society of America
IPC	Infection Prevention and Control
LOT	Length-Of-Therapy
MDRO	Multi Drug-Resistance Organism
MIC	Minimum inhibitory concentration
RCT	Randomized Clinical Trial
WHO	World Health Organisation
WP	Work Package

4. Annexes

4.1 Antibiotic guidance

4.2 eCRF (audit and feedback, antibiotic rounds and antibiotic consumption)



Research and Innovation Action
H2020-SC-1-2020-Single-Stage-RTD

Antibiotic Stewardship (ABS) Basic Intervention Protocol

Annex 4.1

Antibiotic Guidance

Work Package 4

Version 1.4

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Objective and purpose

This guidance document has been produced by the WP4 as part of the basic Antibiotic Stewardship (ABS) implementation strategy within the REVERSE project with the aim of supporting appropriate antimicrobial prescriptions within participating hospitals. The guidance document contains therapeutic indications for the use of antibiotics in the four REVERSE areas (internal medicine, surgery, ICU, onco-haematology) divided into threesections: 1) **Surgical prophylaxis**; 2) **Empiric antibiotic therapy ;** 3) **Treatment of infections sustained by MDR Gram Negatives bacteria.** In line with ABS principle, the document is aimed at improving appropriateness of antibiotic prescriptions and reducing unnecessary antibiotic use. Therefore, narrower spectrum molecules and shorter treatment durations are suggested whenever appropriate. Indications on risk stratification and diagnostic tests to guide antibiotic selection are also provided. All suggested antibiotic choices and durations are in line with the most recent recommendations from national/international guidelines.

The document **is not intended as a substitute for local/national recommendations** in the hospitals that already have antibiotic guidelines in place. The main aim of the document is to promote revision/update of existing protocols, if necessary, facilitate discussion among the ABS teams and local prescribers and to serve as a reference for audit and feedback activities if structured guidelines are not present.
The guidance is presented in the format of tables, organized by suspected or confirmed infection site. The first therapeutic choice is indicated alongside possible alternatives in case of allergies or specific clinical scenarios. The last column contains **the minimum suggested duration** with the suggestion of discussing the case with the ABS team if a prolonged duration is necessary.

All antibiotic dosages reported are applicable to adult patients with preserved renal function. Adjustment based on renal function or patient's weight need to be done by the prescribers following local practice. Especially for the treatment of MDR infections, some of the suggested dosages are higher than those recommended by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) and follow the recent indication from the Infectious Diseases Society of America. Regarding weight, no dosages have been reported for the obese patient. For aminoglycosides it is recommended to use adjusted-body weight for patients weighing more than 120% of their ideal weight.

Severe **allergy to ß-lactams** is defined in the presence of at least one of the following signs or symptoms: airways involvement (wheezing, bronchospasm), anaphylaxis, angioedema, extensive urticaria, hypotension, arrhythmias, shock (IgE-mediated reactions), Stevens-Johnson (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP), haemolytic anemia, interstitial nephritis, hepatitis, serum sickness (non-IgE mediated reactions). In case of severe IgE mediated reactions it would theoretically be possible to use beta-lactams without potential cross-reactivity, while in case of severe non-IgE mediated reactions all beta-lactams should be avoided. For ease of consultation and the difficulty of discriminating the type of reaction, these guidelines suggest an alternative to the beta-lactam in case of serious reactions. If the reactions do not fall within the indicated severity criteria, the suggested alternative beta-lactam (generally a cephalosporin with a different side chain than the suggested first-line antibiotic) can be safely used.

Peri-operative antibiotic prophylaxis in abdominal surgery

Surgical antibiotic prophylaxis must have antimicrobial spectrum that guarantees effectiveness against probable contaminants, generally endogenous germs. The drugs most used for the prophylaxis of surgical interventions are cefazolin or cephalothin, ampicillin-sulbactam, gentamicin and metronidazole.
To be effective, the antibiotics must be administered within 30-60 minutes before the start of the operation, intended as the moment of skin incision. Administering antibiotic prophylaxis too early or late compared to the scheduled time reduces the effectiveness of the prophylaxis and increases the risk of surgical site infections. For most operations there is evidence that a single dose of antibiotics is adequate in reducing the risk of surgical site infections. Further antibiotic administration may be necessary only in the case of prolonged

operations (indications are in the table) and in the case of intra-operative blood losses equal to or greater than 1500mL. In any case, antibiotic prophylaxis in surgery must always be suspended within 24 hours of surgery, regardless of the patients' immune status.

TABLE A: TIMING AND DOSING OF THE MOST COMMON ANTIBIOTICS USED IN SURGICAL PROPHYLAXIS

ANTIBIOTIC	PRE-OPERATIVE DOSE AND TIMING	INTRA-OPERATIVE DOSING*	POST-OPERATIVE DOSING §
Amikacin	**15 mg/kg iv**** within 60 min. preincision	Not needed	**15 mg/kg iv** q24h (reduce if eGFR < 80 ml/min)
Ampicillin-sulbactam	**3 g iv** within 60 min. preincision	**3 g iv** after 2-3h from the 1st dose	**3 g iv** q6h
Amoxicillin-clavulanate	**2.2 g iv** within 60 min. preincision	**2.2 g iv** after 2-3h from the 1st dose	**1.2 / 2.2g iv** q8h
Cefazolin	**2 g iv** (**3 g** if BW > 120 kg) within 60 min. preincision	**2 g iv** after 4h from the 1st dose	**2 g iv** q8h (to be reduced if eGFR <50 ml/min)
Cefuroxime	**1.5 g iv** within 60 min. preincision	**1.5 g iv** after 3h from the 1st dose	**1.5 g iv** q8h
Ceftriaxone	**2 g iv** within 60 min. preincision	Not needed	**2 g iv** q24g
Ciprofloxacin	**400 mg iv/ 500 mg po** 60-120 min preincision	Not needed	**400 mg iv** q8-12h **500 mg po** q12h (to be reduced if eGFR <50 ml/min)
Clindamycin	**900 mg iv** within 60 min. preincision	**900 mg iv** after 6h from the 1st dose	**900 mg iv** q6h
Cotrimoxazole	**1 DS (160/800mg) tb po** **2 vials (80/400mg) iv** within 60 min. preincision	Not needed	**1 DS tb po** q12h **2 vials iv** q 8-12h (to be reduced if eGFR <50 ml/min)
Ertapenem	**1 g iv** within 60 min. preincision	Not needed	**1 g iv q24h**
Gentamicin	**5 mg/kg iv**** within 60 min. preincision	Not needed	**5 mg/kg iv** q24h (if eGFR <80 ml/min) **3 mg/kg iv** q24h (if eGFR 3580 ml/min)
Metronidazole	**500 mg iv** within 60 min. preincision	**500 mg iv** after 4h from the 1st dose	**500 mg** q6h po/iv
Vancomycin	**15 mg/kg iv (administer in at least 30 min)** within 60-120 min. preincision	Not needed	**500 mg iv** q6h (to be reduced if eGFR <50 ml/min)

* always recommended in the case of intra-operative blood losses equal to or greater than 1500mL
** dosing of aminoglycosides for SAP is based on the patient's actual body weight. If the patient's actual weight is more than 20% above ideal body weight (IBW), the dosing weight (DW) can be determined as follows: DW = IBW + 0.4(actual weight – IBW).
§There is no evidence to support the continuation of antibiotic prophylaxis in the post-operative period. All prophylaxis must be suspended within 24 hours of surgery, regardless of the patients immunocompetence status.

TABLE 1. ANTIBIOTIC PROPHYLAXIS OF GASTRODUODENAL SURGERY

INTERVENTION	PRE-OPERATIVE DOSE	INTRA-OPERATIVE DOSE§
HIATAL HERNIA, ESOPHAGEAL DIVERTICULECTOMY, HELLER- DOR PROCEDURE	**Cefazolin iv** 2g	*See table A*
	Alternative to beta-lactams **Clindamycin iv** 900 mg	

ESOPHAGECTOMY (BOTH CERVICAL ANASTOMOSIS AND INTRATHORACIC ANASTOMOSIS)	**Cefazolin iv** 2g *Alternative to beta-lactams* **Clindamycin iv** 900 mg	*See table A*
TOTAL AND PARTIAL GASTRECTOMY	**Amoxicillin-clavulanate iv** 2.2g *Alternative to beta-lactams* **Clindamycin iv** 900 mg + **gentamicin iv** 5mg/kg	*See table A*
ESOPHAGOCOLOPLASTY	**Amoxicillin-clavulanate iv** 2.2g *Alternative to beta-lactams* **Clindamycin iv** 900 mg + **gentamicin iv** 5mg/kg	*See table A*
BARIATRIC SURGERY (ABOVE DUODENUM)	**Cefazolin iv**: • 2g if BMI 30-50 kg/m^2 • 3g if BMI>50 kg/m^2 *Alternative to beta-lactams* **Clindamycin iv** • 900 mg if BMI 30-50 kg/m^2 • 1200 BMI >50 kg/m^2 + **gentamicin iv** • 5mg/kg if BMI>30 kg/m^2 use Adjusted Body Weight*	*See table A*
BARIATRIC SURGERY (BELOW DUODENUM)	**Cefazolin iv**: • 2g if BMI 30-50 kg/m^2 • 3g if BMI>50 kg/m^2 + **metronidazole iv** 1g *Alternative to beta-lactams* **Clindamycin iv**: • 900 mg if BMI kg/m^2 30-50 • 1200 if BMI >50 kg/m^2 + **gentamicin iv:** • 5mg/kg if BMI>30 kg/m^2 use Adjusted Body Weight*	*See table A*
JEJUNOILEAL SURGERY (INCLUDING BILIARY-DIGESTIVE ANASTOMOSES)	**Amoxicillin-clavulanate iv** 2.2g *Alternative to beta-lactams* **Clindamycin iv** 900 mg + **gentamicin iv** 5mg/kg	*See table A*

Note: For clean procedures (e.g., elective vagotomy) the antibiotic prophylaxis is recommended only in the case of an increased risk of infection at the surgical site. Risk factors: reduced gastric acidity, gastroduodenal perforation, reduced gastrointestinal motility, esophageal obstruction, gastric bleeding, obesity, presence of neoplasia.
*ABW: Adjusted Body Weight= Ideal Body Weight (IBW) + 0.4 x (ABW - IBW)
§There is no evidence to support the continuation of antibiotic prophylaxis in the post-operative period. All prophylaxis must be suspended within 24 hours of surgery, regardless of the patients immunocompetence status.

TABLE 2. ANTIBIOTIC PROPHYLAXIS OF PANCREATIC AND BILIARY TRACT SURGERY

INTERVENTION	PRE-OPERATIVE DOSE	INTRA OPERATIVE DOSE§

JEJUNO-ILEAL SURGERY (including biliary-digestive anastomoses)	**Amoxicillin-clavulanate iv** 2.2g *Alternative to beta-lactams* **Clindamycin iv** 900 mg + **gentamicin iv** 5mg/kg	*See table A*
PANCREATIC SURGERY with biliodigestive anastomosis	**Amoxicillin-clavulanate iv** 2.2g *Alternative to beta-lactams* **Clindamycin iv** 900 mg + **gentamicin iv** 5mg/kg	*See table A*
BILIARY TRACT SURGERY in patients with biliary prostheses	**Amoxicillin-clavulanate iv** 2.2g *Alternative to beta-lactams* **Clindamycin iv** 900 mg + **gentamicin iv** 5mg/kg	*See table A*
JEJUNOSTOMY	**Cefazolin iv** 2 g *Alternative to beta-lactams* **Clindamycin iv** 900 mg **Vancomycin iv** 15 mg/kg (maximum 2g to be infused over 60-90 minutes starting 120 minutes before the procedure)	*See table A*
PANCREATIC SURGERY without biliodigestive involvement	**Cefazolin iv** 2 g *Alternative to beta-lactams* **Clindamycin iv** 900 mg + **gentamicin iv** 5mg/kg	*See table A*
BILIARY TRACT SURGERY AND OPEN CHOLECYSTECTOMY	**Cefazolin** iv 2 g *Alternative to beta-lactams* **Clindamycin iv** 900 mg + **gentamicin iv** 5mg/kg	*See table A*
ELECTIVE LAPAROSCOPIC CHOLECYSTECTOMY	**Without risk factors*->** No prophylaxis **With risk factors -> cefazolin iv** 2 g *Alternative to beta-lactams* **Clindamycin iv** 900 mg + **gentamicin iv** 5mg/kg	*See table A*

***Risk factors for infectious complications following laparoscopic cholecystectomy:** episode of biliary colic in the 30 days before the procedure; acute cholecystitis; presence of stones; jaundice; procedure performed urgently; intraoperative gallbladder rupture; risk of conversion to open cholecystectomy

§There is no evidence to support the continuation of antibiotic prophylaxis in the post-operative period. All prophylaxis must be suspended within 24 hours of surgery, regardless of the patients immunocompetence status.

TABLE 3. ANTIBIOTIC PROPHYLAXIS OF COLORECTAL SURGERY

INTERVENTION	PRE-OPERATIVE DOSE	INTRAOPERATIVE DOSE§
HEMORRHOIDECTOMY	**NO**	*See table A*
COLECTOMY	**Amoxicillin-clavulanate iv** 2.2g	*See table A*
	Alternative to beta-lactams **Metronidazole iv** 500 mg + **gentamicin iv** 5 mg/kg	*See table A*
COLORECTAL		*See table A*

SURGERY/ RECTAL SURGERY	**ORAL ANTIBIOTIC PHOPHYLAXIS REGIMENS*:** **Bacitracin/Neomycin po** 25000IU/ 2500IU 1 tb the day before surgery at 8:00/16:00/23.30 + **metronidazole po** 500 mg the day before surgery at 8:00/16:00/23.30 ***Kanamycin po 1 g*** the day before surgery at 8:00/16:00/23.30 + **metronidazole po** 500 mg the day before surgery at 8:00/16:00/23.30 ***Neomycin po 1 g*** the day before surgery at 8:00/16:00/23.30 + **metronidazole po** 500 mg the day before surgery at 8:00/16:00/23.30 **+ Amoxicillin-clavulanate iv** 2.2g *As an alternative to amoxicillin-clavulanate*, **Metronidazole iv** 500 mg + **cefuroxime iv** 1.5 g	
	Alternative to beta-lactams **Metronidazole iv** 500 mg + **gentamicin iv** 5 mg/kg	*See table A*

*** mechanical bowel preparation must always be combined with oral antibiotic prophylaxis.**
§There is no evidence to support the continuation of antibiotic prophylaxis in the post-operative period. All prophylaxis must be suspended within 24 hours of surgery, regardless of the patients' immunocompetence status.

TABLE 4: PROPHYLAXIS IN A PATIENT WITH A POSITIVE RECTAL SWAB UNDERGOING COLO-RECTAL SURGERY

RECTAL SWAB	PRE-PROCEDURE DOSE	INTRA-OPERATIVE§
GRAM-NEGATIVE ESBL-PRODUCERS	*According to the antibiogram, in order of preference* • **Amoxicillin-clavulanate iv** 2.2 g or **Ampicillin/sulbactam iv** 3 g • **Ciprofloxacin iv** 400 mg + **metronidazole iv** 500 mg • **Ertapenem iv** 1 g • **Piperacillin-tazobactam iv** 4,5 g *Alternative to beta-lacatams* **Gentamicin iv** 5 mg/kg + **metronidazole iv** 500 mg *If antibiogram is not available* **Ertapenem iv** 1 g	*See table A*
CARBAPENEM RESISTANT GRAM NEGATIVES (*Klebsiella KPC, Acinetobacter, Pseudomonas*)	**Modifications to SAP are not recommended routinely and should be evaluated on a case-by-case basis. Consider reporting the case to the laboratory to obtain an antibiogram.**	
	As alternative to beta-lactams, consider: **Clindamycin iv** 900 mg + **gentamicin iv** 5 mg/kg	*See table A*
VRE	No recommendations, refer to standard prophylaxis.	

§There is no evidence to support the continuation of antibiotic prophylaxis in the post-operative period. All prophylaxis must be suspended within 24 hours of surgery, regardless of the patients immunocompetence status.

TABLE 5: PROPHYLAXIS FOR ABDOMINAL WALL SURGERY AND SPLENECTOMY

INTERVENTION	PRE-OPERATIVE DOSE	INTRA-OPERATIVE
WITHOUT MESH PLACEMENT	NOT INDICATED	NO

WITH MESH PLACEMENT	**Cefazolin iv** 2g	NO
	Alternatives to beta-lactams **Clindamycin iv** 900 mg ***or*** **Vancomycin iv** 15 mg/kg (maximum 2g to be infused in 60-90 minutes starting 120 minutes before the procedure)	
SPLENECTOMY	**Cefazolin** iv 2g	NO
	Alternatives to beta-lactams **Clindamycin iv** 900 mg ***or*** **Vancomycin iv** 15 mg/kg (maximum 2g to be infused 60-90 minutes starting 120 minutes before the procedure)	

TABLE 6: PROPHYLAXIS OF ENDOSCOPIC AND PERCUTANEOUS DIGESTIVE TRACT PROCEDURES

PROCEDURE	INTERVENTION	PRE-PROCEDURE DOSE*	ALTERNATIVE
ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY (ERCP)	**Complete drainage of the bile duct**	NOT INDICATED	
		If liver cirrhosis, neutropenia, advanced neoplasia **Amoxicillin-clavulanate iv** 2.2 g (60 min. pre-procedure)	*Alternative to beta-lactams* **Ciprofloxacin iv** 400 mg (60-120 min. pre-procedure or 500 mg **po** 60-90 min. pre-procedure)
	Incomplete drainage of the bile duct (e.g., need for stent placement) **Percutaneous Cholangiography/ PTBD**	**Amoxicillin-clavulanate iv** 2.2 g (60 min. pre-procedure)	*Alternative to beta-lactams* **Ciprofloxacin iv** 400 mg (60120 min. pre-procedure or 500 mg **po** 60-90 min. preprocedure)
	Patient with cholangitis	The patient is already on antibiotic therapy; administer the antibiotic treatment 30 minutes before the procedure	
GASTROSCOPY / COLONOSCOPY	**Routine diagnostics (biopsy, polypectomy endoscopy)**	**NOT INDICATED:** endocarditis prophylaxis in patients with mechanical valves or valve malformations it is not indicated in the case of endoscopic procedures of the digestive tract	
	GE bleeding/ esophageal varices ligation with active bleeding/ Mucosal+/- submucosal resections	**Ceftriaxone iv** 1g q24h (60 min. pre-procedure if ligation)	*Alternative to beta-lactams* **Ciprofloxacin iv** 400 mg q12h (60-120 min. pre-procedure if ligation)
LOCO-REGIONAL TREATMENT OF LIVER TUMOR	**TACE/RFTA**	**Amoxicillin-clavulanate iv** 2.2 g (60 min. pre- procedure)	*Alternative to penicillins* **Ceftriaxone iv** 1g 60 minutes pre- procedure
ENDOSCOPIC STOMA PLACEMENT	**PEG**	**Cefazolin iv** 2 g (within 60 minutes of the procedure)	*Alternative to beta-lactams* **Clindamycin iv** 900 mg 60 min. pre-procedure
		If MRSA colonization **Vancomycin iv** 15 mg/kg (maximum 2g to be infused 60-90 minutes starting 120 minutes before the procedure)	

*** In the case of CR-GNB colonization, the evidence is not sufficient to modify the standard recommendations.**

Empiric antibiotic therapy in hospitalized patients

TABLE 1: EMPIRICAL THERAPY OF URINARY TRACT INFECTIONS

SITE OF INFECTION	CLINICAL STATUS	ANTIBIOTIC	ALTERNATIVES (in order of preference)	DURATION
LOWER URINARY TRACT INFECTION In the absence of signs and symptoms of a systemic infection)	**Uncomplicated***	**Nitrofurantoin po** 100 mg q6h for 5 days *Only for female sex*	**Fosfomycin trometamol po** 3g single dose	Specific for every single molecule
	Complicated*	**Preferable to wait for the urine culture results, especially if history of MDR UTI in the previous 12 months.** If empirical therapy is necessary→ **Fosfomycin trometamol** 3 g single dose	**Trimethoprim/ sulfamethoxazole po** DS tb q12h **Amoxicillin-clavulanate** 1 g (**po**)/1.2 g (iv) q12h	**7 days**
PYELONEPHRITIS/ UROSEPSIS With signs and symptoms of systemic infection)	**Uncomplicated***	**Cefotaxime iv** 2 g q8h *or* **ceftriaxone iv** 2 g q24h	**Gentamicin iv** 5 mg/kg q24h **Levofloxacin iv/po** 750 q24	**7 days** (5 days for gentamicin)
	Complicated* No risk factor for MDRO§	**Piperacillin-tazobactam iv** 4.5 g q6h	**Ceftazidime iv** 2 g q8h **Gentamicin iv** 5 mg/kg q24h	**7-14 days**
	Complicated* Risk factor for MDRO§	**Piperacillin-tazobactam iv** 4.5 g q6h + **gentamicin** 5 mg/kg q24h	*If history of UTI due to ESBL organisms in the previous 12 months* **Meropenem iv** 1 g q8h	**7-14 days**
ACUTE PROSTATITIS		**Trimethoprim/ sulfamethoxazole po** DS tb q12h	**Ciprofloxacin po** 500 mg q12h	**14 days**

*** Defining factors for COMPLICATED UTIs (the presence of one single factor is sufficient):**
- Indwelling urinary catheter, ureteral stent or urinary diversion
- Obstructive uropathy (benign prostatic hypertrophy, neurogenic bladder, kidney stones, neoplasms) - Vesicoureteral reflux or other functional abnormalities
- Medical history of radiotherapy or a urinary tract procedure
- Chronic kidney failure, transplants, diabetes mellitus, immunosuppression - Diabetes, menopausal status, male sex

§ Risk factors for MDRO: admitted from a LTCF, hospitalization in the preceding 3 months, antibiotic use in the preceding 3 months (fluoroquinolones, cephalosporins)

TABLE 2: ASYMPTOMATIC BACTERIURIA

Definition: presence of one or more positive urine cultures with a bacterial load of at least 10^5 CFU/ml in the absence of signs or symptoms of infection (with or without pyuria).

WHEN TO TREAT	WHEN NOT TO TREAT
- Before surgical procedures involving the urinary tract: positioning or replacement of nephrostomy/stent - Endoscopic procedures that require an interruption of the continuity of the mucosa - Pregnancy	- Diabetes - Kidney transplant more than 1 month - Presence of indwelling urinary catheter, ureteral stent or urinary diversion - Neutropenia - Obstructive uropathy or abnormal functionality of the urinary tract

NOTE: The presence of pyuria alone on the chemical-physical test or a urine stick test is not an indication to send a urine culture.

TABLE 3: COMMUNITY ACQUIRED PNEUMONIA

CLINICAL PRESENTATION	RISK FACTORS	ANTIBIOTIC	ALTERNATIVES	DURATION
Non severe *(as an example: SMART-COP<5*, other risk scores can be applied according to local practice, i.e. Pneumonia Severity Index, CURB-65)*	**No comorbidities §**	**Amoxicillin po** 1g q8h	*Alternative to beta-lactams or clinical suspicion of atypical pneumonia* **Doxycycline po** 100 mg q12h **Azithromycin po** 500 mg q24h *	**5 days** (7-10 days in case of *Legionella)*
	Comorbidities §	**Amoxicillinclavulanate** 1 g (**po**)/ 1.2 g (**iv**) q8h + **clarithromycin po** 500 mg q12h	*Alternative to penicillins* **Ceftriaxone iv** 2 g q24h + **clarithromycin po** 500 mg q12h	
			Alternative to beta-lactams + macrolide **Levofloxacin po/iv** 750 mg q24h	
	Suspected aspiration pneumonia	**Amoxicillinclavulanate iv** 1.2 g q8h	*Alternative to amoxicillinclavulanate* **Ceftriaxone iv** 2 g q24h + **metronidazole po/iv** 500 mg q6h	
Severe *SMART-COP ≥5** **Additional steroids:** * Always to be considered in patients receiving intensive support *[Hydrocortisone 200 mg/day in IC for 4 days; or methylprednisolone 0.5 mg/kg q12h for 5 days]* * In all other patients, evaluate risk-benefit. Evidence of greater benefit for smokers and with decreasing age. Dosages differ in the literature *[use for example methylprednisolone 0.5 mg/kg q12h]*	**No risk factors for MDRO****	**Ceftriaxone iv** 2 g q24h + **clarithromycin po** 500 mg q12h	*Alternative to beta-lactams + macrolide* **Levofloxacin po/iv** 750 mg q24	**7 days** (1421 days in the case of Legionella)
	Risk factors for *Pseudomonas aeruginosa***	**Cefepime iv** 2 g q8h + **clarithromycin po** 500 mg q12h	*Alternative to beta-lactams + macrolides* **Ciprofloxacin iv** 400 mg q8 *or* **levofloxacin po/iv** 750 mg q24h	
	Risk factors for MRSA**	**Piperacillintazobactam iv** 4.5 g q6h + **clarithromycin po** 500 mg q12h + **linezolid po/iv** 600 mg q12h	*Alternative to beta-lactam + macrolides* **Levofloxacin po/iv** 750 mg q24 *Alternative to linezolid* **Vancomycin iv** 25 mg/kg loading dose followed by 15-20 mg/kg q12h	
	Flu season	Add oseltamivir po 75 mg q12h		**5-10 days**
	Aspiration pneumonia	**Piperacillintazobactam iv** 4.5 g q8h	*Alternative to piperacillintazobactam* **Ertapenem iv** 1 g q24h	**7 days**

SMART COP calculation (pt< 50y/o)		SMART COP calculation (pt≥ 50y/o)	
S Systolic blood pressure < 90 mmHg	2 points	**S** Systolic blood pressure < 90 mmHg	2 points
M Multilobar infiltrates	1 point	**M** Multilobar infiltrates	1 point
A Albumin < 3.5 g/dl	1 point	**A** Albumin < 3.5 g/dl	1 point
R Respiratory rate ≥ 25/min	1 point	**R** Respiratory rate ≥ 30/min	1 point
T Tachycardia ≥125 bpm	1 point	**T** Tachycardia ≥125 bpm	1 point
C Confusion (new onset)	1 point	**C** Confusion (new onset)	1 point
O Oxygen saturation PaO2 <70 mmHg or SatO2 ≤93% or P/F< 333	2 points	**O** oxygen saturation PaO2 <60 mmHg or SatO2 ≤90% or P/F< 250	2 points
P pH <7.35	2 points	**P** pH <7	2 points

§ Comorbidities: chronic lung, kidney, heart, liver diseases, neoplasms, diabetes, alcohol abuse, asplenia;
* Azithromycin not recommended as monotherapy if *Streptococcus pneumoniae* resistance is > 25%

* Risk factors for P. aeruginosa: bronchiectasis/cystic fibrosis, isolation of P. aeruginosa on broncho-alveolar lavage within the last 3 months or immunosuppression; Risk factors for MRSA: drug addiction, flu season or cavitated lesion, close contact with animals, competitive team sports, travel to South-East Asia or USA.

TABLE 4: CRONIC OBSTRUCTIVE PULMUNARY DISEASE EXACERBATION

SYMPTOMS	CLINICAL SEVERITY	ANTIBIOTIC	ALTERNATIVE	DURATION
Only 1 cardinal symptom*	-	No antibiotic therapy		
2 cardinal symptoms* (one of which is sputum purulence)	**MILD (at least three out of five)** - VAS dyspnea < 5 - Respiratory Rate <24/min - Heart Rate <95, - SatO2 room air (or chronic O2) > 92% or change >/=3%, - CRP <10 mg/l	**Amoxicillinclavulanate** 1 g (**po**) / 1.2 g (**iv**) q8h	*Alternative to amoxicillin* **Clarithromycin po** 500 mg q12h *or* **doxiciline po** 100 mg q12h *If risk factor for P. aeruginosa§* **Ciprofloxacin po** 750 mg q12h	**5 days**
2 cardinal symptoms* (one of which is sputum purulence) **AND/OR mechanical ventilation**	**MODERATE (at least three out of five)** - VAS dyspnea > 5 - Respiratory Rate ≥ 24/min - Heart Rate ≥ 95, - SatO2 room air (or chronic O2) < 92% or change > 3%, - CRP > 10 mg/l - PaO2<60mmHg e/o PaCO2 > 45 mmHg with no acidosis **SEVERE** PaCO2 > 45 mmHg AND pH < 7.35	**Piperacillintazobactam iv** 4,5 g q6h	*Alternative to penicillin* **Ceftazidime ev** 2g q8h *Alternative to betalactams* **Ciprofloxacin iv 400mg q8h**	**5 days**

* Increased dyspnea/ increased sputum / purulent sputum.
§ Risk factors for P. aeruginosa: previous infections, severe COPD, bronchiectasis

TABLE 5: HOSPITAL ACQUIRED PNEUMONIA

CLINICAL PRESENTATION	ANTIBIOTIC	ALTERNATIVES	DURATION
NON-SEVERE *No sign of sepsis*	**Ceftazidime iv** 2 g q8h or **cefepime iv** 2 g q8h **§**	**Piperacillin-tazobactam iv** 4.5 g q6h *Alternative to beta-lactams* **Levofloxacin po/iv** 750 mg q24h	**7 days**
SEVERE *Sign of sepsis and/or rapid progression*	**Meropenem iv** 1 g q8h **+ linezolid iv** 600 mg q12h* *If hemodynamically instable, risk factors for MDR P. aeruginosa* **§** *or prolonged*	*Alternative to linezolid* **Vancomycin iv*** 25 mg/kg loading dose followed by 15-20 mg/kg q12h *Alternative to amikacin* **Ciprofloxacin iv** 400 mg q8	**7-14 days**

	admission **+ amikacin iv 15 mg/kg q24h**		
	Colonization with Carbapenem resistant-GNB	**See Guidelines on treatment of MDR-GNB infections**	

***Early stop of anti-MRSA antibiotic is possible if respiratory samples or/and nasal screening are negative for MRSA**

§ Coverage for *P. aeruginosa* should be tailored to local epidemiology. We suggest a threshold of 20% for nonsevere and 5-10% for severe infections. **Risk factors for *P. aeruginosa*:** bronchiectasis/cystic fibrosis, isolation of *P. aeruginosa* on BAL within the last 3 months or immunosuppression

TABLE 6: VENTILATOR ASSOCIATED PNEUMONIA (VAP)

Definition:
- Admitted/intubated for > 48h
- New finding of consolidation on chest X-ray + at least one of the following:
  - Fever >38°C or hypothermia <36°C
  - Purulent secretions
  - Leukocytosis/leukopenia
  - Worsening of PaO2/FiO2

SEVERITY	MDR RISK FACTORS	ANTIBIOTIC	DURATION
NON-SEVERE APACHE II □ 15]	**No risk factors for MDROs* AND negative/unknown colonization status §**	**Piperacillin-tazobactam iv** 4.5 g q6h in 3h prolonged infusion *Alternative to piperacillin-tazobactam:* **Cefepime iv** 2 g q8h	**7 days**
	Risk factors for MDROs* OR known colonization with MRSA, ESBL, CR-GNB	**Piperacillin-tazobactam iv** 4.5 g q6h in 3h prolonged infusion + **amikacin iv** 15mg/kg q24h *If known MRSA colonization:* + **linezolid po/iv** 600mg q12h *Alternative to piperacillin-tazobactam:* **Cefepime iv** 2 g q8h	
	No risk factors for MDROs AND negative/unknown colonization status §	**Ceftazidime iv** 2 g q8h + **amikacin iv** 15mg/kg q24h + **linezolid po/iv** 600mg q12h → consider stopping if nasal swab/BAL culture is negative for MRSA	

SEVERE [APACHE II>15] or NEUTROPENIA	**Risk factors for MDROs* OR colonization with MRSA or ESBL**	**Meropenem iv** 1 g q8h in 3h prolonged infusion + **linezolid po/iv** 600mg q12h → consider stopping if nasal swab/BAL culture is negative for MRSA *If high rates of DTR-Pseudomonas, as alternative to meropenem* **Ceftolozane-tazobactam iv** 2.5 g q8h
	Colonization with CR-GNB	**→ See Guidelines on treatment of MDRGNB infections**

*** Risk factors for MDROs:** Patient coming from a long-term care facility, hospitalization in the last three months, treatment with cephalosporins or fluoroquinolones in the past three months, known/previous colonization with MDR-GNB in the last year, prolonged ICU stay (>7 days).

§ Coverage for *P. aeruginosa* should be tailored to local epidemiology. We suggest a threshold of 20% for non-severe and 5-10% for severe infections

TABLE 7: EMPIRICAL THERAPY OF INTRA-ABDOMINAL INFECTIONS

TYPE OF INFECTION	CLINICAL STATUS	ANTIBIOTIC	ALTERNATIVE	DURATION
COMMUNITY ACQUIRED INTRA-ABDOMINAL INFECTIONS	**Hemodynamically stable patient**	**Amoxicillin-clavulanate iv** 1.2 g q8h	**Ceftriaxone iv** 2g q24h + **metronidazole po/iv** 500 mg q6h	Mildmoderate severity with adequate *source control* **4 days after the surgery** High severity with adequate *source control* **7 days**
			Alternative to beta-lactams **ciprofloxacin** iv 400 mg q8h + **metronidazole po/iv** 500 mg q6 h	
	Hemodynamically unstable patient	**Piperacillin-tazobactam iv** 4.5 g q6h	*Alternative to penicillin or risk factors for ESBLs** **Meropenem iv** 1 g q8h	
INTRA-ABDOMINAL INFECTIONS NOSOCOMIAL/ POST-SURGERY	**Hemodynamically stable patient****	**Piperacillin-tazobactam iv** 4.5g q8h *If MRSA colonization or **in the absence** of clinical improvement after 72hrs* + **vancomycin iv** 25-30 mg/kg followed by 15-20 mg/kg q12h	*Alternative to piperacillintazobactam* **Ceftazidime iv** 2g q8h + **metronidazole po/iv** 500 mg q6 h	
			Alternative to beta-lactams **Ciprofloxacin iv** 400 mg q8h + **metronidazole po/iv** 500 mg q6 h	
			*If risk factors for ESBLs** **meropenem iv** 1g q8h	
	Hemodynamically unstable patient	**Meropenem iv** 1 g q8h + **vancomycin** iv 25-30 mg/kg followed by 15-20 mg/kg q12h + **caspofungin iv** 70 mg loading dose, then 50 mg q24h	*Alternative to vancomycin* **Daptomycin iv** 8mg/kg q24h	
	Non necrotic	Antibiotic therapy not recommended		

ACUTE PANCREATITIS	**Acute necrotic pancreatitis**** **Pseudocysts or abscesses secondary to necrotic pancreatitis****	**Piperacillin-tazobactam iv** 4.5 g q8h	*Alternative to piperacillintazobactam* **Meropenem iv** 1 g q8h *Alternative to beta-lactams* **Ciprofloxacin iv 400 mg** q8h + **metronidazole po/iv** 500 mg q6h	**5 days**
SPONTANEOUS BACTERIAL PERITONITIS	**Community acquired**	**Amoxicillin-clavulanate iv** 2.2 g q8h	**Cefotaxime iv** 2 g q8h *or* **ceftriaxone** 2g q24h *Alternative to beta-lactams* **Ciprofloxacin iv 400 mg** q8h	**5 days**
	Hospitalized patient	**Piperacillin-tazobactam iv** 4.5 g q8h *If MRSA colonization or **in the absence** of clinical improvement after 72hrs* + **vancomycin iv** 25-30 mg/kg followed by 15-20 mg/kg q12h	*If hemodynamic instability* **Meropenem iv** 1 g q8h + **daptomycin iv** 8mg/kg q24h + **anidulafungin iv** 200 mg loading dose, then 100 mg q24h	

*Risk factors for ESBLs: patient transferred from a long-term care facility; hospitalization in the last three months; treatment with cephalosporins or fluroquinolones in the last three months.
** *Empiric* antifungal coverage with an echinocandin is recommended in hemodynamically unstable patients. Beta-D-glucan can be performed at the same time and, if negative, can be used to stop the empirical treatment, given its high negative predictive value in low prevalence settings.

TABLE 8: CLOSTRIDIOIDES DIFFICILE INFECTION (CDI)

DEFINITION: clinical symptoms and positivity of microbiological investigations (GDH antigen+ and toxin+)
NOTE 1: ONLY test patients with new onset of diarrhea, defined as the passage of at least 3 loose stools/day.
NOTE 2: NOT INDICATED to repeat the test during the treatment to verify the negative result or decide on isolation.
NOTE 3: Contact isolation should be continued for AT LEAST 48 hours after the resolution of diarrhea. Evaluate the continuation of isolation until discharge in wards with a high incidence of CDI.

EPISODE	CLINICAL PRESENTATION	ANTIBIOTIC	ALTERNATIVE	DURATION
FIRST EPISODE	**Not severe** (<15000 WBC, and creatinine <1.5 mg/dl)	**Vancomycin po** 125 mg q6h **+ discontinue** the administration of other antibiotics as soon as possible	*If outpatient management, consider:* **Metronidazole po** *500 mg q8h* *If high risk of recurrence*, consider:* **Fidaxomicin po** 200 mg q12h	**10 days**
	Severe (≥15000 WBC and/or creatinine ≥1.5 mg/dl)	**Vancomycin po** 125 mg q6h **+ discontinue** the administration of other antibiotics as soon as possible	*If high risk of recurrence*, consider:* **Fidaxomicin po** 200 mg q12h **+ discontinue** the administration of other antibiotics as soon as possible.	

FIRST RECURRENCE §	**Severe and not severe**	**Fidaxomicin po** 200 mg q12h per 10 days **+ discontinue** the administration of other antibiotics as soon as possible *Consider adding:* **Bezlotoxumab iv** 10 mg/kg as a single administration in patients at higher risk for recurrence*	**vancomycin po prolonged administration** 125 mg q6h for 10 days q12h for 7 days, q24h for 7 days, q48-72h for 2-8 weeks **+ discontinue** the administration of other antibiotics as soon as possible	Specific for each single molecule
SECOND OR SUBSEQUENT RECURRENCE	**Severe and not severe**	**Fidaxomicin po** 200 mg q12h for 10 days **+ discontinue** the administration of other antibiotics as soon as possible **Vancomycin po prolonged administration** 125 q6h for 10 days q12h for 7 days, q24h for 7 days, q48-72h for 2-8 weeks **+ discontinue** the administration of other antibiotics as soon as possible	**vancomycin po** 125 mg q6 for 10 days and then rifaximin 400 mg q8h for 20 days Evaluate options and indications of fecal transplant **+ discontinue** the administration of other antibiotics as soon as possible	Specific for each single molecule
ANY EPISODE	**Fulminant** *shock, hypotension, paralytic ileus, or toxic megacolon*	**Vancomycin po** 500 mg q6h (via NG) **+ metronidazole iv** (500 mg q8h) **+ discontinue** the administration of other antibiotics as soon as possible **+ surgical evaluation** if ileus/toxic megacolon	*If paralytic ileus, add* **+ vancomycin** via rectal administration (500 mg in 100 ml saline solution 0.9% q6h) *Alternative to iv metronidazole* **Tigecycline iv** 100 mg loading dose, then 50 mg q12h	**14 days**

*__High risk of recurrence:__ immunocompromised, impossible to stop antibiotics, age > 65, ongoing PPI
§ __Recurrence:__ every episode occurring < 8 wks from the previous episode

TABLE 9: EMPIRICAL THERAPY OF SKIN AND SOFT TISSUE INFECTIONS

TYPE OF INFECTION	CLINICAL PRESENTATION	ANTIBIOTIC	ALTERNATIVES	DURATION
ERYSIPELAS/CELLULITIS	**Mild/moderate**	**Amoxicillin-clavulanate po** 1g every 8h (or 1.2 g q8h iv)	**Penicillin G iv 3MU iv q8h**	**5 days**
			Cefazolin iv 1 g q8h	
			Trimethoprim/ sulfamethoxazole po DS tb q12h	
			Alternative to beta-lactams **vancomycin iv** 15 mg/kg q12h	
	Severe §	**Amoxicillin-clavulanate iv** 2.2 g q8h	*Alternative to penicillins* **Ceftriaxone iv 2g** + **vancomycin iv** 25-30 mg/kg	

		+ **vancomycin iv** 25-30 mg/kg followed by 15-20 mg/kg q12h (target steady-state concentration 1520mg/ml)	*If patient is diabetic* **Piperacillin-tazobactam iv** 4.5 g q6h + **vancomycin iv** 25-30 mg/kg	
			If orbital involvement: **Ceftriaxone iv** 2 g q24h **+ metronidazole iv** 500 mg q6h **+ vancomycin iv** 25-30 mg/kg	**7 days**
NECROTIZING FASCIITIS	**Any clinical presentation**	**Piperacillin-tazobactam iv** 4.5 g q6h **+ linezolid po/iv** 600 mg q12h **+ ALWAYS surgical debridement** and send sample for culture examination	*Alternative to penicillins* **Meropenem iv** 1 g q8 h *Alternative to linezolid* **daptomycin iv** 8 mg/kg q24h *If suspected streptococcal toxic syndrome*, add clindamycin iv 600 mg q6h	**10 days**
PRESSURE SORES/ CHRONIC VASCULAR ULCERS	**Mild infection/ superficial**	**Antibiotic therapy not recommended****		
	Moderate infection/ Severe with systemic involvement	**Piperacillin-tazobactam iv** 4.5 g q8h **+ ALWAYS surgical debridement** and send sample for culture examination	*If MRSA colonization, lack of response after 72 hours, signs of sepsis, add:* + **vancomycin iv** 25-30 mg/kg followed by 15-20 mg/kg q12h (target steady-state concentration 15-20mg/ml)	**5 days**

§ Severe: fever, rapid progression of erythema, extensive erythema, involvement of the hand or the face
* If risk factors for MRSA: iv drug user, close contact with animals, competitive team sports, local epidemiology
** Remove infected tissues/necrosis; remove the source of infection (reposition the patient/ do not apply weight onto the affected limb/ revascularization); appropriate dressings (e.g., sulfadiazine cream, no benefit in administering topical antibiotics compared to new antiseptics and advanced dressings).

TABLE 10: SEPTIC ARTHRITIS

RISK FACTORS	ANTIBIOTIC	ALTERNATIVES	DURATION
No risk factors	***Surgical drainage for source control and sampling collection*** **+ vancomycin iv** 25-30 mg/kg followed by 15-20 mg/kg q12h + **ceftriaxone iv** 2g q24h	*Alternative to vancomycin* **Daptomycin iv** 8 mg/kg q24h *Alternative to beta-lactams* **ciprofloxacin** 400 mg q8h ev	**7-21 days**
Risk factors (intravenous drug user, immunocompromised, post-trauma)	***Surgical drainage for source control and sampling collection*** **+ vancomycin iv** 25-30 mg/kg followed by 15-20 mg/kg q12h + **ceftazidime iv** 2g q24h		

TABLE 11: TRAUMATIC WOUND (no fracture)

INITIAL CARE	ANTIBIOTIC PROPHYLAXIS	DURATION

• **Irrigation** • **Debridement** • **Consider delayed surgical closure (>48h) if highly contaminated or open wound > 6 hours** • **Verify tetanus immunization**	**To be considered ONLY in high-risk wounds* AND to be administered as soon as possible, ideally within 2 hours from surgical care.** **Amoxicillin-clavulanate iv** 2.2 g (q8h) *Alternative to beta-lactams* **clindamycin iv** 600 q8h *if heavily contaminated, add: +* **gentamicin iv** 5 mg/kg q24h	**To be continued ONLY in contaminated wounds OR in wound bites** **3-5 days**

*** RISK OF INFECTION:**
WOUND TYPE: linear wounds (low); tear/burn/bruise (high); penetrating wounds (high); traumatic compression wounds (high); bite wounds (high); macroscopically contaminated wounds (high); presence of foreign body (high); wounds with diastasis of the margins (high); deep tissue involvement (high)
WOUND LOCALIZATION: good vascularization (e.g., head, neck) (low); Highly colonized by commensal flora, e.g., oral mucosa, groin, axilla (high); Poor vascularization, for example. E.g., hand, foot, leg, and forearm (high)
PATIENT'S RISK FACTORS: children, adolescents, and adults (low); Elderly (>65) (high); Immunocompromised, e.g., steroid trp, HIV, splenectomy, immunosuppressants, chemotherapy (high); Diabetes (high); Vasculopathies (high)

TABLE 12: MANAGEMENT OF OPEN FRACTURES

TYPE OF FRACTURE	ANTIBIOTIC	DURATION
Open fractures Type I-II* (any size, minimal to moderate contamination, adequate tissue coverage)	To be administered as soon as possible, ideally within 6 hours **Cefazolin iv** 2g q8h (3g if BW > 120 kg) *As alternative to beta-lactams* **Clindamycin iv** 600 q8h	24 hours
Type III* open fractures (any size, severe contamination)	To be administered as soon as possible, ideally within 6 hours **Amoxicillin-clavulanate iv** 2.2 g (q8h) *As alternative to penicillins or water contamination* **Ceftazidime iv** 2g q8h As alternative to beta-lactams **Clindamycin iv** 600 q6h + **gentamicin iv** 5 mg/kg q24h	72 hours

***Gustillo-Anderson Classification**

TABLE 13: FEVER IN ASPLENIC PATIENTS

CLINICAL PRESENTATION		ANTIBIOTIC	ALTERNATIVES	DURATION
FEVER IN PATIENTS WITH ASPLENIA (functional or post-surgical)	**Hemodynamically stable patients**	**Ceftriaxone iv** 2 g (within 2h from onset of symptoms)	**Piperacillin-tazobactam iv** 4.5g q6h *Alternative to beta-lactams* **levofloxacin po/iv** 500 mg q12h	7 days
	Hemodynamically unstable patients	**Cefepime iv** 2 g q8h + **vancomycin iv** 25-30 mg/kg followed by 15-20 mg/kg q12h (target steadystate concentration 1520mg/ml)	*Alternative to cefepime* **piperacillin-tazobactam iv** 4.5g q6h ***or* meropenem iv** 2 g q8h	10 days

TABLE 14: CENTRAL VENOUS CATHETER (CVC) INFECTIONS

CLINICAL PRESENTATION	ANTIBIOTIC	DURATION
Hemodynamically stable patients	**CVC removal** **+ vancomycin iv** 25-30 mg/kg followed by 15-20 mg/kg q12h (target steady-state concentration 15-20mg/ml) *If femoral CVC, add* **piperacillin-tazobactam iv** 4.5 g q6h	**5-7 days (depending on the isolate)**
Hemodynamically unstable patients	**Urgent CVC removal** **+ daptomycin iv** 8 mg/kg q24h *or* **vancomycin iv** 25-30 mg/kg followed by 15-20 mg/kg q12h **+ meropenem iv** 1 g q8h **+ caspofungin* iv** 70 mg loading dose, then 50 mg q24h	**Depending on the isolates and potential complications**
*Empiric antifungal coverage with an echinocandin is recommended in hemodynamically unstable patients. Beta-D-glucan can be performed at the same time and, if negative, can be used to stop the empirical treatment, given its high negative predictive value in low prevalence settings		

TABLE 15: SEPSIS OF UNKNOWN ORIGIN

RISK FACTORS	ANTIBIOTIC	ALTERNATIVES
Absence of risk factors for ESBLs*	**Piperacillin-tazobactam iv** 4.5 g q6h in prolonged infusion 3h + **vancomycin iv** 25-30 mg/kg followed by 15-20 mg/kg q12h	*Alternative to penicillins* **Cefepime iv 2g q8h**
		Alternative to vancomycin **daptomycin iv** 8-10 mg/kg q24h *or, if pulmonary source suspected* **linezolid po/iv** 600 mg q12h
Risk factors for ESBLs*	**Meropenem iv** 2 g q8h in prolonged infusion 3h + **vancomycin iv** 25-30 mg/kg followed by 15-20 mg/kg q12h	*Alternative to beta-lactams + / - amikacin* **Gentamicin iv** 3-5 mg/kg **iv** q24h
	If shock is present, add: **Amikacin iv** 20 mg/kg loading dose, followed by 15 mg/kg q24h	*Alternative to vancomycin* **daptomycin iv** 8-10 mg/kg q24h *or, if pulmonary source suspected* **linezolid po/iv** 600 mg q12h
Known colonization/ previous infection with Carbapenemresistant Enterobacterales (CRE, e.g., KPC)	**Ceftazidime-avibactam iv** 2.5 g q8h **+ vancomycin** iv 25-30 mg/kg followed by 15-20 mg/kg q12h *If possible abdominal source,* **+ metronidazole iv** 500 mg q8h	*Alternative to ceftazidime-avibactam + metronidazole* **meropenem-vaborbactam iv** 4g q8h
		Alternative to ceftazidime-avibactam + metronidazole **Gentamicin iv** 3-5 mg/kg **iv** q24h **+ meropenem iv** 2 g q8h in prolonged infusion 3h
	If known colonization with a metallo-beta lactamase + **aztreonam iv** 2 g q8h, infused in 3 hours, possibly at the same time as ceftazidime-avibactam	*Alternative to vancomycin* **+ daptomycin iv** 8-10 mg/kg q24h *or, if pulmonary source suspected* **linezolid po/iv** 600 mg q12h
Known colonization/ previous infection with Difficult-to-treat	**Ceftolozane-tazobactam iv** 3g q8h in 3 hours	*Alternative to ceftolozane-tazobactam* **Ceftazidime-avibactam iv** 2.5 g q8h **+ metronidazole iv** 500 mg q8h

Pseudomonas aeruginosa	**+ vancomycin iv** 25-30 mg/kg followed by 15-20 mg/kg q12h	*Alternative to ceftolozane-tazobactam* **Amikacin iv** 20 mg/kg loading dose, followed by 15 mg/kg q24h **+ meropenem iv** 2 g q8h in prolonged infusion 3h
		Alternative to vancomycin **+ daptomycin iv** 8-10 mg/kg q24h *or, if pulmonary source suspected* **linezolid** 600 mg q12h
Known colonization/ previous infection with Carbapenemresistant *Acinetobacter*	**Colistin iv** 9 MU loading dose followed by 5,5 MU q12h + **meropenem iv** 2 g q8h in prolonged infusion 3h **+ vancomycin iv** 25-30 mg/kg followed by 15-20 mg/kg q12h	*Alternative to meropenem* **ampicillin-sulbactam iv** 9 g (6/3) q8h in prolonged infusion over 3 hours **+ amikacin iv** 20 mg/kg loading dose, followed by 15 mg/kg q24h ***or**, if known resistance to ampicillin-sulbactam* **cefiderocol iv** 2g q8h in prolonged infusion over 3 hours
		Alternative to vancomycin **+ daptomycin iv** 8-10 mg/kg q24h ***or**, if pulmonary source suspected* **linezolid iv** 600 mg q12h
Risk factors for invasive Candida§ infection / absence of clinical response within 72 hours	+ **caspofungin iv** 70 mg loading dose, then 50 mg q24h	*Alternative to caspofungin* **Micafungin iv** 100 mg q24 **or anidulafungin iv** 200 mg loading dose followed by 100 mg q24h

*__Risk factors for ESBLs__: patient transferred from a long-term care facility; hospitalization in the last three months; treatment with cephalosporins or fluroquinolones in the last three months, colonization/infections with ESBLs in the previous 12 months.
§__Risk factors for Candida__: CVC carrier, TPN, diabetes mellitus, transplant recipient, major surgery in particular abdominal surgery in the last 6 months, broad spectrum antibiotic therapy in the previous 30 days, multi-site colonization by *Candida*.

TABLE 17: FEBRILE NEUTROPENIA

DEFINITION: a single oral temperature measurement ≥ 38.3°C or an oral temperature >38°C lasting more than one hour+ an absolute neutrophil count <500 cells/microL. LOW RISK: expected duration <7 days, no kidney or liver function abnormalities.
HIGH RISK NEUTROPENIA: <100 cells/microL, expected duration >7 days, alterations in liver or kidney functions, mucositis, progressive neoplasia.
TREATMENT DURATION: If negative cultures treat until afebrile for >72h, irrespective of neutrophil count

CLINICAL STATUS	RISK FACTORS	ANTIBIOTIC	ALTERNATIVES
Stable patient Low risk neutropenia	**Possible outpatient management** *(good compliance, ED access 24/7)*	**Ciprofloxacin po** 750 q12h **+ amoxicillin-clavulanate po** 1g q12h	*Alternative to amoxicillinclavulanate* **clindamycin po** 300 mg q6h
FEBRILE NEUTROPENIA **Stable patient High risk neutropenia**	**Negative/unknown colonization status/ no risk factors for MDRO***	**Piperacillin-tazobactam iv** 4.5 g q6h	*Alternative to penicillins* **Cefepime iv** 2 g q8h
	Colonization/ previous ESBLs infection	**Meropenem iv** 1g q8h	*Alternative to carbapenems* **Piperacillin-tazobactam iv** 4.5 g q6h **+ amikacin iv** 15 mg/kg q24h
	Risk factors for MDRO*	**Piperacillin-tazobactam iv** 4.5 g q6h + **amikacin iv** 15 mg/kg q24h	*Alternative to penicillins* **Cefepime iv** 2 g q8h **+ amikacin iv** 15 mg/kg q24h
	No clinical response at 48h **or known risk factors for MRSA***	+ **vancomycin iv** 25-30 mg/kg followed by 15-20 mg/kg q12h	*Alternative to vancomycin* **Daptomycin iv** 8-10 mg/kg q24h
	No clinical response 96h after starting therapy	*Consider adding antifungal treatment based on clinical evolution and microbiological diagnostics (beta-D-glucan, galattomannan, CT-scan…) and evaluate antibiotic escalation if patient deteriorates*	

FEBRILE NEUTROPENIA **Sign of sepsis or rapid progression**	**No known colonisation for CRGNB**	**Meropenem iv** 2 g every 8 h in a prolonged infusion 3h **+ amikacin iv** 15 mg/kg q24h **+ vancomycin iv** 25-30 mg/kg followed by 15-20 mg/kg q12h **+ caspofungin iv** 70 mg loading dose, then 50 mg q24h
	Known colonization/ previous infection with CR- GNB	➔ *Always consider the addition of aminoglicosides based on local susceptibility rates (i.e.* **+ amikacin iv** 15 mg/kg q24h)**.** ➔ *Always add coverage for MDR-gram positive and Candida* **+ vancomycin iv** 25-30 mg/kg followed by 15-20 mg/kg q12h **+ caspofungin iv** 70 mg loading dose, then 50 mg q24h ➔ ***SELECT THE BETA-LACTAM BASED ON THE KNOWN/MOSTLIKELY RESISTANCE MECHANISM:***
	KPC,OXA-48	**Ceftazidime-avibactam iv** 2.5 g every 8h *If suspected abdominal source, add* **metronidazole iv** 500 mg q8h *Alternative to ceftazidime-avibactam* **meropenem/vaborbactam iv** 4g q8h *(not active on OXA-48) or* **imipenem-relebactam iv** 1.25 g iv q6h
	MBL (VIM, NDM…)	**Ceftazidime-avibactam iv** 2.5 g q8h **+ aztreonam iv** 2 g q8h, infused in 3 hours, possibly at the same time as ceftazidime-avibactam *or* **cefiderocol iv** 2 g q8h
	DTR-Pseudomonas	**Ceftolozane-tazobactam iv** 3g q8h *If suspected abdominal source, add* **metronidazole iv** 500 mg q8h
	CR-Ab	**Cefiderocol 2 g iv q8h** + **amikacin iv** 15 mg/kg q24h *or* **meropenem iv** 2 g q8 h in a prolonged infusion 3h **+ colistin iv** 9 mln IU loading dose followed by 5,5 mln IU q12h

*__Risk factors for MDRO:__ patient transferred from another hospital/long-term care facility, treatment with cephalosporins or fluoroquinolones in the past three months, known/previous colonization with CR-GNB in the last year, hospital stay >7 days.
**__Risk factors for MRSA:__ previous infections/colonization with MRSA, high suspicion of catheter related infection (i.e. fever and chills after line use), skin and soft tissue infections, high local prevalence of MRSA carriers.

Targeted therapy of Multi-Drug-Resistant Gram-Negative Infections

Severe Infection are intended as those infections which present an increased risk of an unfavourable outcome, defined as death or short-and long-term debilitating consequences, based on three parameters: - *Clinical presentation:* patient with sepsis or septic shock according to the Sepsis-3 criteria (Singer M, et al. JAMA 2016);

- *Site of infection:* an infection in whose site of origin is associated, more frequently than other sites, with an unfavourable outcomes (e.g. lung infections compared to infections originating from the urinary tract as identified in the INCREMENT score, Palacios-Baena ZR, et al. JAC 2017) or an infection in which it is not possible to implement adequate *source control* of the infection site such as complex intra-abdominal infections or the presence of device that cannot be removed),
- *Risk of progression:* presence of severe immunosuppression (e.g., transplant patients, cancer patients undergoing chemotherapy, neutropenic patients)

Non-severe infections are intended as infection generally associated with favourable progress, defined based on the following parameters:

- *Clinical presentation:* patient without signs of sepsis or septic shock.
- *Site of infection:* urinary infection, skin and soft tissue infection, or infection where optimal *source control* of the infection site is performed (e.g abdominal infection after adequate source control, CVC-related bacteraemia after removal of the catheter)
- *No risk of unfavourable progression:* absence of severe impairment of immune system.

***Antibiotic of 'conventional use'* (ACU):** antibiotics approved before 2010 with action against Multi-resistant Gram-negative bacteria: aminoglycosides, colistin, tigecycline and carbapenems.

Difficult to treat Pseudomonas aeruginosa: strains resistant to ceftazidime, piperacillin-tazobactam, cefepime, aztreonam, meropenem, imipenem-cilastatin, levofloxacin, and ciprofloxacin.

Enterobacterales resistant to third generation cephalosporins (3GCRE)

ENTEROBACTERALES RESISTANT TO THIRD GENERATION CEPHALOSPORINS			
UNCOMPLICATED URINARY TRACT INFECTIONS		**Dosage**	**Note**
First line	**Nitrofurantoin**	Modified release 100 mg **po** q12h Immediate release 50-100 mg **po** q6h	Only if susceptible
	Fosfomycin trometamol	3 g **po** - single dose	
Second line	**Cotrimoxazole**	160mg/800 mg **iv/po** q12h	
	Amikacin	15 mg/kg/dose **iv** - single dose	
	Gentamicin	5 mg/kg/dose **iv** - single dose	
	Amoxicillinclavulanate	1 g (equals to 875 mg amoxicillin) **po** q8-12h	Do not prescribe if Amp-C producing bacteria or resistance mechanism is unknown
	Levofloxacin	750 mg **iv/po** q24h	
	Ciprofloxacin	400 mg **iv** q8h-q12h 500-750 mg **po** q12h	

ENTEROBACTERALES RESISTANT TO THIRD GENERATION CEPHALOSPORINS			
COMPLICATED URINARY INFECTIONS		**Dosage**	**Note**
First line	**Fosfomycin iv**	16-18 g **iv** (to divide q6h-q8h)	In the absence of renal and cardiac functional impairments (*carbapenem-sparing treatment*), and if caused by *E. coli*
	Amikacin	20 mg/kg/dose **iv** 1st dose followed by 15 mg/kg q24h	Maximum duration: 7 days
	Gentamicin	7 mg/kg/dose **iv** 1st dose followed by 5 mg/kg q24h	
Second line	**Levofloxacin**	750 mg **iv** q24h	
	Ciprofloxacin	400 mg **iv** q8h-q12h	
	Co-trimoxazole	160mg/800 mg **iv/po** q12h	
	Amoxicillinclavulanate	2.2 g **iv** q8h	Do not prescribe if AmpC producing bacteria or

	Ampicillinsulbactam	3g **iv** q6h	resistance mechanism is unknown
Alternative ***If the first and second line not possible***	**Piperacillintazobactam**	4.5 g q6h iv, infused in 3 hours	
	Ertapenem	1 g **iv** q24h	
	Meropenem	1 g **iv** q8h	
	Cefepime	2 g **iv** q8h, infused in 3 hours	Only if Amp-C producing bacteria

ENTEROBACTERALES RESISTANT TO THIRD GENERATION CEPHALOSPORINS			
SKIN AND SOFT TISSUE INFECTIONS AND INFECTIONS WITH OPTIMAL SOURCE CONTROL		**Dosage**	**Note**
First line	**Amoxicillin-clavulanate**	2.2 g **iv** q8h	Do not prescribe if AmpC producing bacteria or resistance mechanism is unknown
	Ampicillin-sulbactam	3g **iv** q6h	
Second line	**Piperacillin-tazobactam**	4.5 g **iv** q6h, infused in 3 hours	
	Levofloxacin	750 mg **iv** q24h	
	Ciprofloxacin	400 mg **iv** q8h-q12h	
	Cefepime	2 g iv q8h, infused in 3 hours	Only if AmpC producing bacteria
Alternative ***If first line or second line not possible***	**Ertapenem**	1 g **iv** q24h	
	Meropenem	1 g **iv** q8h	
	Fosfomycin iv	12-18 g **iv** (to be divided q8h-q12h)	Only in combination

ENTEROBACTERALES RESISTANT TO THIRD GENERATION CEPHALOSPORINS			
SEPSIS AND SEPTIC SHOCK, PNEUMONIA, ABDOMINAL INFECTION WITH SUBOPTIMAL SOURCE CONTROL, INFECTION OF THE CNS		**Dosage**	**Note**
First Line	**Imipenem-cilastatin**	500 mg **iv** q6h	
	Meropenem	1 g **iv** q8h	
Second Line	**Cefepime**	2 g iv q8h, infused in 3 hours	Only if Amp-C producing bacteria
	Fosfomycin iv	12-24 g **iv** q8h-q12h	Only in combination

Alternative *if first and second line not possible*	**Ceftazidime-avibactam**	2.5 g **iv** q8h	In order to preserve these molecules for other MDR pathogens, use only if other therapeutic options are not available
	Ceftolozane-tazobactam	3 g **iv** q8h	

Infections due to Carbapenem resistant Enterobacterales (CRE)

CARBAPENEM RESISTANT ENTEROBACTERALES			
UNCOMPLICATED URINARY INFECTIONS		**Dosage**	**Note**
First line	**Amikacin**	15 mg/kg/dose **iv** - single dose	
	Gentamicin	5 mg/kg/dose **iv** - single dose	
	Nitrofurantoin	Modified release 100 mg **po** q12h Immediate release 50-100 mg **po** q6h	
	Co-trimoxazole	160mg/800 mg **iv/po** q12h	
Second Line	**Fosfomycin trometamol**	3 g **po** - single dose or 2 doses (2nd dose after 48h)	
Alternative ***If first line or second line not available***	**Meropenem**	2 g **iv** q8h	If MIC < 2 mg/l
	Ceftazidimeavibactam	2.5 g **iv** q8h	
	Meropenemvaborbactam	4 g **iv** q8h	
	Cefiderocol	2 g **iv** q8h	
	Colistin	Loading dose 9 mln IU **iv** followed by 4.5 mln IU **iv** q12h	
	Tigecycline	Loading dose 100 mg iv, followed by 50 mg **iv** q12h	

CARBAPENEM RESISTANT ENTEROBACTERALES			
COMPLICATED URINARY TRACT INFECTIONS		**Dosage**	**Note**
First line	**Co-trimoxazole**	8-12 mg/kg/daily (based on trimethoprim) **iv/po** divided q8-12h (maximum dose of trimethoprim/daily: 960 mg)	
	Amikacin	20 mg/kg/dose **iv** 1st dose followed by 15 mg/kg q24h	Maximum duration 7 days

	Gentamicin	7 mg/kg/dose **iv** 1st dose followed by 5 mg/kg q24h	
	Meropenem	2 g **iv** q8h, infused in 3 hours	If MIC < 2 mg/l
Second Line	**Ceftazidimeavibactam**	2,5 g **iv** q8h	
	Meropenemvaborbactam	4 g **iv** q8h	
Alternative *if first or second line not possible*	**Cefiderocol**	2 g **iv** q8h	
	Colistin	Loading dose 9 mln IU **iv** followed by 4.5 mln IU **iv** q12h	
	Tigecycline	Loading dose 100 mg **iv**, followed by 50 mg **iv** q12h	

CARBAPENEM RESISTANT ENTEROBACTERALES			
SKIN AND SOFT TISSUE INFECTIONS AND INFECTIONS WITH OPTIMAL SOURCE CONTROL		**Dosage**	**Note**
First Line	**Meropenem**	2 g **iv** q8h, infused in 3 hours	Only if MIC < 2 mg/l
	Ceftazidime-avibactam	2.5 g **iv** q8h	
	Meropenemvaborbactam	4 g **iv** q8h	
	Tigecycline	Loading dose 100 mg **iv**, followed by 50 mg **iv** q12h	In intra-abdominal infections
Alternative *If first and second line not possible*	**Amikacin**	20 mg/kg/dose **iv** 1st dose followed by 15 mg/kg q24h	
	Gentamicin	7 mg/kg/dose **iv** 1st dose followed by 5 mg/kg q24h	
	Colistin	Loading dose 9 mln IU **iv** followed by 4.5 mln IU **iv** q12h	

CARBAPENEM RESISTANT ENTEROBACTERALES

SEPSIS AND SEPTIC SHOCK, PNEUMONIA, ABDOMINAL INFECTIONS WITH SUBOPTIMAL SOURCE CONTROL, CNS INFECTIONS§		Dosage	Note
First line	**Meropenem**	2 g **iv** q8h, infused in 3 hours	If MIC for meropenem < 2 mg/l
	Ceftazidime-avibactam	2.5 g **iv** q8h	
	Meropenemvaborbactam	4 g **iv** q8h	**Not active** on OXA-48 producing bacteria
Second Line	**Amikacin**	20 mg/kg/dose **iv** 1st dose followed by 15 mg/kg q24h	Severe urinary infections and only in combination with another antibiotic of 'conventional use'*
	Gentamicin	7 mg/kg/dose **iv** 1st dose followed by 5 mg/kg q24h	
	Colistin	Loading dose 9 mln IU **iv** followed by 5.5 mln IU **iv** q12h	Only in combination with another antibiotic of 'conventional use'*
	Fosfomycin iv	12-24 g **iv** q8h -q12h	
	Tigecycline	Loading dose 100 mg **iv**, followed by 50 mg **iv** q12h	Severe abdominal infections and only in combination with another antibiotic of 'conventional use'*
	Meropenem	2 g **iv** q8h, infused in 3 hours	If MIC >2 mg/l and ≤ 8 mg/l in combination with another antibiotic of 'conventional use'*
Alternative ***If first and second line not possible***	**Cefiderocol**	2 g **iv** q8h	Severe urinary infections and lung infections with documented production of metallo-ß-lactamase
	Ceftazidime-avibactam + aztreonam	Ceftazidime-avibactam: 2.5 g **iv** q8h + aztreonam: 2 g **iv** q8h, infused in 3 hours, possibly at the same time as ceftazidime-avibactam	If documented production of metallo- ß -lactamase

§ combination treatment should be evaluated, especially if first line antibiotic are not available (consider also intrathecal administration of colistin)

***Antibiotic of conventional use:** antibiotics approved before 2010 with action against MDR-GN bacteria: aminoglycosides, colistin, tigecycline and carbapenems. To be selected based on antibiotic susceptibility results.

Infections due to Pseudomonas Difficult to Treat (Difficult-to-treat - DTR)

PSEUDOMONAS DTR		
UNCOMPLICATED URINARY TRACT INFECTIONS		**Dosage**
First Line	**Amikacin**	15 mg/kg/dose **iv** - single dose
	Gentamicin	5 mg/kg/dose **iv** - single dose

Second line	**Colistin**	Loading dose 9 mln IU **iv** followed by 4.5 mln IU **iv** q12h
	Ceftolozane-tazobactam	1.5 g **iv** q8h
	Ceftazidime-avibactam	2.5 g **iv** q8h
	Imipenem-cilastatin-relebactam	1.25 mg **iv** q6h
	Cefiderocol	2 g **iv** q8h

PSEUDOMONAS DTR			
COMPLICATED URINARY INFECTIONS		**Dosage**	**Note**
First Line	**Amikacin**	20 mg/kg/dose **iv** 1st dose followed by 15 mg/kg q24h	Maximum duration: 7 days
	Gentamicin	7 mg/kg/dose **iv** 1st dose followed by 5 mg/kg q24h	
	Ceftolozane-tazobactam	1.5 g **iv** q8h	
Second Line	**Ceftazidime-avibactam**	2.5 g **iv** q8h	
	Imipenem-cilastatin-relebactam	1.25 g **iv** q6h	
	Cefiderocol	2 g **iv** q8h	

PSEUDOMONAS DTR		
SKIN AND SOFT TISSUE INFECTIONS AND INFECTIONS WITH OPTIMAL SOURCE CONTROL		**Dosage**
First Line	**Ceftolozane-tazobactam**	1.5 g **iv** q8h
Second Line	**Ceftazidime-avibactam**	2.5 g **iv** q8h
	Imipenem-cilastatin-relebactam	1.25 g **iv** q6h
Alternative ***If first and second line not available***	**Cefiderocol**	2 g **iv** q8h
	Colistin	Loading dose 9 mln IU **iv** followed by 4.5 mln IU **iv** q12h

PSEUDOMONAS DTR		
SEPSIS AND SEPTIC SHOCK, PNEUMONIA, ABDOMINAL INFECTIONS WITH SUBOPTIMAL SOURCE CONTROL, CNS INFECTIONS	**Dosage**	**Note**

First line	**Ceftolozane-tazobactam**	3 g **iv** q8h	
Second Line	**Ceftazidime-avibactam**	2.5 g **iv** q8h	
	Imipenem-cilastatin-relebactam	1.25 g **iv** q6h	
Alternative ***If first and second line are not available***	**Cefiderocol**	2 g **iv** q8h	Severe urinary tract infections and lung infections with documented production of metallo-beta-lactamases
	Colistin	Loading dose 9 mln IU **iv** followed by 4.5 mln IU **iv** q12h Intrathecal treatment: 125000 IU of colistimethate sodium	Only in another antibiotic of 'conventional use', in meningitis and ventriculitis combine intrathecal therapy with intravenous therapy

Infections due to Carbapenem-resistant Acinetobacter baumannii (CRAB)

CARBAPENEM-RESISTANT ACINETOBACTER BAUMANNII		
UNCOMPLICATED URINARY TRACT INFECTIONS		**Dosage**
First Line	**Ampicillin-sulbactam**	3 g **iv** q4h
Second Line	**Colistin**	Loading dose 9 mln IU **iv** followed by 4.5 mln IU iv q12h
	Amikacin	15 mg/kg/dose **iv** - single dose
	Gentamicin	5 mg/kg/dose **iv** - single dose
Alternative ***If first or second line not available***	**Cefiderocol**	2 g **iv** q8h

CARBAPENEM-RESISTANT ACINETOBACTER BAUMANNII		
NON SEVERE INFECTIONS (COMPLICATED URINARY TRACT INFECTIONS, INFECTIONS WITH OPTIMAL SOURCE CONTROL)		**Dosage**
First line	**Ampicillin-sulbactam**	3 g **iv** q4h
Second line	**Tigecycline**	Loading dose 100 mg **iv**, followed by 50 mg **iv** q12h
	Colistin	Loading dose 9 mln IU **iv** followed by 4.5 mln IU **iv** q12h
Alternative ***If first or second line not possible***	**Cefiderocol**	2 g **iv** q8h

CARBAPENEM-RESISTANT ACINETOBACTER BAUMANNII			
SEPSIS AND SEPTIC SHOCK, PNEUMONIA, ADBOMINAL INFECTIONS WITH SUBOPTIMAL SOURCE CONTROL, CNS INFECTIONS		**Dosage**	**Note**
First line	**Ampicillin-sulbactam**	9 g **iv** q8h infused in 4 hours / 27 g **iv** q24h in continuous infusion	Only in combination with another antibiotic of 'conventional use'*
	Colistin	Loading dose 9 mln IU **iv** followed by 5.5 mln IU **iv** q12h	
	Tigecycline	Loading dose 100 mg **iv** followed by 50 mg **iv** q12h	
Second line	**Cefiderocol**	2 g **iv** q8h	

*Antibiotic of conventional use: **antibiotics approved before 2010 with action against Multi-resistant Gram-negative bacteria: aminoglycosides, colistin, tigecycline and carbapenems. To be selected based on antibiotic susceptibility results.**

List of abbreviations

3GCRE	Third generation cephalosporins
ABS	Antimicrobial stewardship
ACU	Antibiotic of Conventional Use
BAL	Bronchoalveolar Lavage
CDI	Clostridium difficile Infection
COPD	Chronic obstructive pulmonary disease
CR-GNB	Carbapenem-resistent Gram negative bacteria
CRAB	Carbapenem-resistant Acinetobacter baumannii
CRE	Carbapenem-resistent Enterobacterales
CURB-65	Confusion, Uremia, Respiratory rate, BP, age ≥ 65 years
CVC	Central venous catheter
DRESS	Drug reaction with eosinophilia and systemic symptoms
DS	double strength
DTR	Difficult to treat
eGFR	estimated Glomerular Filtration Rate
EMA	European Medicines Acency
ERCP	Endoscopic Retrograde Cholangiopancreatography
ESBL	Extended-spectrum beta-lactamase
FDA	Food and Drug Administration
GDH	Glutamate dehydrogenase
GI	Gastrointestinal tract
GN	Gram-negative
ICU	Intensice care unit
IU	International Unit
iv	Intravenous administration
KPC	Klebsiella pneumoniae carbapenemase
LTCF	Long term care facility
MDRO	Multi-drug resistant organism
MRSA	Methicillin-resistant staphylococcus aureus
PEG	Percutaneous Endoscopic Gastrotomy
po	Oral administration, by month
PPI	Proton Pump Inhibitor
PTBD	Percutaneous transhepatic biliary drainage
q6h/q8h/q12h/q24h	Every 6/8/12/24 hours
qSOFA/SOFA	Quick Sequential Organ Failure Assessment/Sequential Organ Failure Assessment
RFTA	Radiofrequency Thermal Ablation
SJS	Stevens-Johnson
SMART-COP	Systolic blood pressure, Multilobar infiltrates, Albumin, Respiratory rate, Tachycardia, Ponfusion, Oxygen, and (p)H
TACE	Trans arterial chemoembolization
TB	Tablet
TEN	toxic epidermal necrolysis
TPN	Total parenteral nutrition
UTI	Urinary tract infection

VAS	visual analog scale
VRE	Vancomycin-resistant Enterococci
WBC	White blood cell count

Source documents

Surgical prophylaxis

1. Bratzler, Dale W., et al. "Clinical practice guidelines for antimicrobial prophylaxis in surgery." Surgical infections 14.1 (2013): 73-156.
2. Berríos-Torres SI, Umscheid CA, Bratzler DW, et al. Centers for Disease Control and Prevention Guideline for the Prevention of Surgical Site Infection, 2017. JAMA Surg 2017; 152:784.
3. Blumenthal KG, Ryan EE, Li Y, et al. The Impact of a Reported Penicillin Allergy on Surgical Site Infection Risk. Clin Infect Dis 2018; 66:329.
4. Cohen ME, Salmasian H, Li J, et al. Surgical Antibiotic Prophylaxis and Risk for Postoperative Antibiotic-Resistant Infections. J Am Coll Surg 2017; 225:631.
5. Global guidelines for the prevention of surgical site infection. World Health Organization, 2018
6. Mazuski JE, Tessier JM, May AK, et al. The Surgical Infection Society Revised Guidelines on the Management of Intra-Abdominal Infection. Surgical Infections 2017; 18(1):1-76.
7. Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis 2016;62(4):e1-50.
8. Sartelli M, Chichom-Mefire A, Labricciosa FM, Hardcastle T, Abu-Zidan FM, Adesunkanmi AK, et al. The management of intraabdominal infections from a global perspective: 2017 WSES guidelines for management of intra-abdominal infections. World J Emerg Surg. 2017;12:29.
9. Weber WP, Mujagic E, Zwahlen M, et al. Timing of surgical antimicrobial prophylaxis: a phase 3 randomised controlled trial. Lancet Infect Dis 2017;17:605.
10. Garner JS. CDC guideline for prevention of surgical wound infections, 1985. Supersedes guideline for prevention of surgical wound infections published in 1982. (Originally published in November 1985). Revised. Infect Control 1986;7:193-200.
11. Righi E, Mutters NT, Guirao X, Del Toro MD, Eckmann C, Friedrich AW, Giannella M, Kluytmans J, Presterl E, Christaki E, Cross ELA, Visentin A, Sganga G, Tsioutis C, Tacconelli E. ESCMID/EUCIC clinical practice guidelines on perioperative antibiotic prophylaxis in patients colonized by multidrug-resistant Gram-negative bacteria before surgery. Clin Microbiol Infect. 2023 Apr;29(4):463-479. doi: 10.1016/j.cmi.2022.12.012. Epub 2022 Dec 22. PMID: 36566836.

Empirical therapy

1. Bonkat G, Pickard R, Bartoletti R, Cai T, Bruyére F, Geerlings SE, et al. EAU Guidelines on Urological Infections 2022. European Association of Urology Guidelines 2022 Edition.
2. Caron F, Galperine T, Flateau C, Azria R, Bonacorsi S, Bruyere F, et al. Practice guidelines for the management of adult community-acquired urinary tract infections. Med Mal Infect. 2018;48(5):327-58.
3. Hooton TM, Bradley SF, Cardenas DD, Colgan R, Geerlings SE, Rice JC, et al. Diagnosis, prevention, and treatment of catheterassociated urinary tract infection in adults: 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America. Clin Infect Dis. 2010;50(5):625-63.
4. Mull N FA, Dutcher L, Patel N, Major-Joynes B, Dy S, Alby K, O'Donnell JA, Pegues DA, Mitchell MD, Cavella A, Umscheid CA. Development and Implementation of an Evidence-Based Pathway for the Evaluation of Catheter Associated UTI (Cauti) in an Academic Health System. Journal of Hospital Medicine. 2016;11.
5. Smelov V, Naber K, Bjerklund Johansen TE. Improved Classification of Urinary Tract Infection: Future Considerations. European Urology Supplements. 2016;15(4):71-80.
6. Nicolle LE, Gupta K, Bradley SF, Colgan R, DeMuri GP, Drekonja D, et al. Clinical Practice Guideline for the Management of Asymptomatic Bacteriuria: 2019 Update by the Infectious Diseases Society of Americaa. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2019.
7. Metlay JP, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K, et al. Diagnosis and treatment of adults with comunity-acquired pneumonia. An official clinical practice guideline of the American Thoracic Society and Infecious Diseases Society of America. Am J Respir Crit Care Med 2019; 200(7):e45-e67.
8. Torres A, Niederman MS, Chastre J, Ewig S, Fernandez-Vandellos P, Hanberger H, et al. International ERS/ESICM/ESCMID/ALAT guideline for the management of hospital-acquired pneumonia and ventilator-associated pneumonia. Eur Respir J 2017; 50:1700582
9. Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney DA, Palmer LB, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis 2016; 63(5): e61-111
10. Charles PG, Wolfe R, Whitby M, Fine MJ, Fuller AJ, Stirling R, et al. SMART-COP: a tool for predicting the need for intensive respiratory or vasopressor support in community-acquired pneumonia. Clin Infect Dis. 2008;47(3):375-84.
11. Egger ME, Myers JA, Arnold FW, Pass LA, Ramirez JA, Brock GN. Cost effectiveness of adherence to IDSA/ATS guidelines in elderly patients hospitalized for Community-Aquired Pneumonia. BMC Med Inform Decis Mak. 2016;16:34. 29.
12. Venkatesan, Priya. "GOLD COPD report: 2023 update." The Lancet Respiratory Medicine 11.1 (2023): 18.30.
13. Celli, Bartolome R., et al. "An updated definition and severity classification of chronic obstructive pulmonary disease exacerbations: the Rome proposal." American Journal of Respiratory and Critical Care Medicine 204.11 (2021): 1251-1258.

14. Dever JB, Sheikh MY. Review article: spontaneous bacterial peritonitis--bacteriology, diagnosis, treatment, risk factors and prevention. Aliment Pharmacol Ther. 2015;41(11):1116-31.
15. van Prehn J, Reigadas E, Vogelzang EH et al. European Society of Clinical Microbiology and Infectious Diseases: 2021 update on the treatment guidance document for Clostridioides difficile infection in adults. Clin Microbiol Infect 2021; 27 Suppl 2: S1–S21. https://doi.org/10.1016/j.cmi.2021.09.038
16. Kelly, Colleen R. MD, AGAF, FACG1; Fischer, Monika MD, MSc, AGAF, FACG2; Allegretti, Jessica R. MD, MPH, FACG3; LaPlante, Kerry PharmD, FCCP, FIDSA4; Stewart, David B. MD, FACS, FASCRS5; Limketkai, Berkeley N. MD, PhD, FACG (GRADE Methodologist)6; Stollman, Neil H. MD, FACG7. ACG Clinical Guidelines: Prevention, Diagnosis, and Treatment of Clostridioides difficile Infections. The American Journal of Gastroenterology 116(6):p 1124-1147, June 2021. | DOI: 10.14309/ajg.0000000000001278
17. McDonald LC, Gerding DN, Johnson S, Bakken JS, Carroll KC, Coffin SE, et al. Clinical Practice Guidelines for Clostridium difficile Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis. 2018;66(7):987-94.
18. Sartelli M, Chichom-Mefire A, Labricciosa FM, Hardcastle T, Abu-Zidan FM, Adesunkanmi AK, et al. The management of intraabdominal infections from a global perspective: 2017 WSES guidelines for management of intra-abdominal infections. World J Emerg Surg. 2017;12:29.
19. Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJ, Gorbach SL, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the infectious diseases society of America. Clin Infect Dis. 2014;59(2):147-59.
20. Hoff WS1, Bonadies JA, Cachecho R, Dorlac WC. East Practice Management Guidelines Work Group: update to practice management guidelines for prophylactic antibiotic use in open fractures. J Trauma. 2011 Mar;70(3):751-4. doi: 10.1097/TA.0b013e31820930e5.
21. Hauser CJ1, Adams CA Jr, Eachempati SR; Council of the Surgical Infection Society Surgical Infection Society guideline: prophylactic antibiotic use in open fractures: an evidence-based guideline. Surg Infect (Larchmt). 2006 Aug;7(4):379-405.
22. Prevaldi et al. Management of traumatic wounds in the Emergency Department: position paper from the Academy of Emergency Medicine and Care (AcEMC) and the World Society of Emergency Surgery (WSES)World Journal of Emergency Surgery (2016) 11:30
23. Mermel LA, Allon M, Bouza E, Craven DE, Flynn P, O'Grady NP, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2009;49(1):1-45.
24. Yahav D, Franceschini E, Koppel F, Turjeman A, Babich T, Bitterman R, et al. Seven versus 14 days of antibiotic therapy for uncomplicated Gram-negative bacteremia: a noninferiority randomized controlled trial. Clin Infect Dis.2019; 69(7):1091-1098 25. Havey TC, Fowler RA, Daneman NJCC. Duration of antibiotic therapy for bacteremia: a systematic review and meta-analysis. 2011;15(6):R267.
26. Hawkey PM, Warren RE, Livermore DM, McNulty CAM, Enoch DA, Otter JA, et al. Treatment of infections caused by multidrugresistant Gram-negative bacteria: report of the British Society for Antimicrobial Chemotherapy/Healthcare Infection Society/British Infection Association Joint Working Party. J Antimicrob Chemother. 2018;73(suppl_3):iii2-iii78.
27. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):801-10.
28. Evans, Laura, et al. "Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021." Critical care medicine 49.11 (2021): e1063-e1143.
29. Pappas P.G., Kauffman C.A., Andes D.R.,Clancy C.J., Marr K.A, Ostrosky-Zeichner L., et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. Clin.Infect.Dis.2016; 62(4):e1-e50.
30. Cornely OA, Bassetti M, Calandra T, Garbino J, Kullberg BJ, Lortholary O, et al. ESCMID* guideline for the diagnosis and management of Candida diseases 2012: non-neutropenic adult patients. Clin Microbiol Infect. 2012;18 Suppl 7:19-37.
31. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, et al. Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer: 2010 Update by the Infectious Diseases Society of America. Clinical Infectious Diseases. 2011;52(4):e56-e93.
32. Averbuch D, Orasch C, Cordonnier C, Livermore DM, Mikulska M, Viscoli C, et al. European guidelines for empirical antibacterial therapy for febrile neutropenic patients in the era of growing resistance: summary of the 2011 4th European Conference on Infections in Leukemia. Haematologica. 2013;98(12):1826-35.
33. Ullmann AJ, Akova M, Herbrecht R, Viscoli C, Arendrup MC, Arikan-Akdagli S, et al. ESCMID* guideline for the diagnosis and management of Candida diseases 2012: adults with haematological malignancies and after haematopoietic stem cell transplantation (HCT). Clin Microbiol Infect. 2012;18 Suppl 7:53-67.

Treatment of MDR-GNB infections

1. Carrara E, Grossi PA, Gori A, Lambertenghi L, Antonelli M, Lombardi A, Bongiovanni F; AIFA-OPERA Working Group; Magrini N, Manfredi C, Stefani S, Tumbarello M, Tacconelli E. How to tailor recommendations on the treatment of multi-drug resistant Gramnegative infections at country level integrating antibiotic stewardship principles within the GRADE-ADOLOPMENT framework. Lancet Infect Dis. 2023 Sep 4:S1473-3099(23)00435-8. doi: 10.1016/S1473-3099(23)00435-8. Epub ahead of print. PMID: 37678308.
2. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America AntimicrobialResistant Treatment Guidance: Gram-Negative Bacterial Infections. Infectious Diseases Society of America 2022; Version 1.1. Available at https://www.idsociety.org/practice- guideline/amr-guidance/.
3. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America Gui- dance on the Treatment of AmpC β-lactamase-Producing Enterobacterales, Carbapenem-Resistant Acinetobacter baumannii, and Stenotrophomonas maltophilia Infections. Infectious Diseases Society of America 2022; Version 2.0. Available at https://www.idsociety.org/practice-guideline/amr-guidance-2.0/.
4. Paul M, Carrara E, Retamar P, Tängdén T, Bitterman R, Bonomo RA, de Waele J, Daikos GL, Akova M, Harbarth S, Pulcini C, Garnacho-Montero J, Seme K, Tumbarello M, Lindemann PC, Gandra S, Yu Y, Bassetti M, Mouton JW, Tacconelli E,

RodríguezBaño J. European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant Gram-negative bacilli (endorsed by European society of intensive care medicine). Clin Microbiol Infect. 2022 Apr;28(4):521- 547. doi: 10.1016/j.cmi.2021.11.025. Epub 2021 Dec 16. PMID: 34923128.

5. Hawkey PM, Warren RE, Livermore DM, McNulty CAM, Enoch DA, Otter JA, Wilson APR. Treatment of infections caused by multidrug-resistant Gram-negative bacteria: report of the British Society for Antimicrobial Chemotherapy/ Healthcare Infection Society/British Infection Association Joint Working Party. J Antimicrob Chemother. 2018 Mar 1;73(suppl_3):iii2-iii78. doi: 10.1093/jac/dky027. PMID: 29514274.
6. Pouch SM, Patel G; AST Infectious Diseases Community of Practice. Multidrug-resistant Gram-negative bacterial infections in solid organ transplant recipients-Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019 Sep;33(9):e13594. doi: 10.1111/ctr.13594. Epub 2019 Jul 22. PMID: 31102483.
7. Rello J, Solé-Lleonart C, Rouby JJ, Chastre J, Blot S, Poulakou G, Luyt CE, Riera J, Palmer LB, Pereira JM, Felton T, Dha- nani J, Bassetti M, Welte T, Roberts JA. Use of nebulized antimicrobials for the treatment of respiratory infections in invasively mechanically ventilated adults: a position paper from the European Society of Clinical Microbiology and Infectious Diseases. Clin Microbiol Infect. 2017 Sep;23(9):629-639. doi: 10.1016/j.cmi.2017.04.011. Epub 2017 Apr 13. PMID: 28412382.
8. Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney DA, Palmer LB, Napolitano LM, O'Grady NP,Bartlett JG, Carratalà J, El Solh AA, Ewig S, Fey PD, File TM Jr, Restrepo MI, Roberts JA, Waterer GW, Cruse P, Knight SL, Brozek JL. Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis. 2016 Sep 1;63(5):e61-e111. doi: 10.1093/cid/ciw353. Epub 2016 Jul 14. Erratum in: Clin Infect Dis. 2017 May 1;64(9):1298. Erratum in: Clin Infect Dis. 2017 Oct 15;65(8):1435. Erratum in: Clin Infect Dis. 2017 Nov 29;65(12):2161. PMID: 27418577; PMCID: PMC4981759.
9. Tsuji BT, Pogue JM, Zavascki AP, Paul M, Daikos GL, Forrest A, Giacobbe DR, Viscoli C, Giamarellou H, Karaiskos I, Kaye D, Mouton JW, Tam VH, Thamlikitkul V, Wunderink RG, Li J, Nation RL, Kaye KS. International Consensus Guidelines for the Optimal Use of the Polymyxins: Endorsed by the American College of Clinical Pharmacy (ACCP), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Infectious Diseases Society of America (IDSA), International Society for Anti-infective Pharmacology (ISAP), Society of Critical Care Medicine (SCCM), and Society of Infectious Diseases Pharmacists (SIDP). Pharmacotherapy. 2019 Jan;39(1):10-39. doi: 10.1002/phar.2209. PMID: 30710469; PMCID: PMC7437259.
10. Tunkel AR, Hasbun R, Bhimraj A, Byers K, Kaplan SL, Scheld WM, van de Beek D, Bleck TP, Garton HJL, Zunt JR. 2017 Infectious Diseases Society of America's Clinical Practice Guidelines for Healthcare-Associated Ventriculitis and Meningitis. Clin Infect Dis. 2017 Mar 15;64(6):e34-e65. doi: 10.1093/cid/ciw861. PMID: 28203777; PMCID: PMC5848239.
11. Hou SY, Wu D, Feng XH. Polymyxin monotherapy versus polymyxin-based combination therapy against carba- penem-resistant Klebsiella pneumoniae: A systematic review and meta-analysis. J Glob Antimicrob Resist. 2020 Dec;23:197-202. doi: 10.1016/j.jgar.2020.08.024. Epub 2020 Oct 19. PMID: 33091620.
12. Agyeman AA, Bergen PJ, Rao GG, Nation RL, Landersdorfer CB. A systematic review and meta-analysis of treatment outcomes following antibiotic therapy among patients with carbapenem-resistant Klebsiella pneumoniae infections. Int J Antimicrob Agents. 2020 Jan;55(1):105833. doi: 10.1016/j.ijantimicag.2019.10.014. Epub 2019 Nov 12. PMID: 31730892.
13. Fiore M, Alfieri A, Di Franco S, Pace MC, Simeon V, Ingoglia G, Cortegiani A. Ceftazidime-Avibactam Combination Therapy Compared to Ceftazidime-Avibactam Monotherapy for the Treatment of Severe Infections Due to Carbapenem-Resistant Pathogens: A Systematic Review and Network Meta-Analysis. Antibiotics (Basel). 2020 Jul 7;9(7):388. doi: 10.3390/antibiotics9070388. PMID: 32645986; PMCID: PMC7400227.
14. Effah CY, Drokow EK, Agboyibor C, Liu S, Nuamah E, Sun T, Miao L, Wang J, Xu Z, Wu Y, Zhang X. Evaluation of the Therapeutic Outcomes of Antibiotic Regimen Against Carbapenemase-Producing Klebsiella pneumoniae: A Systematic Review and Meta-Analysis. Front Pharmacol. 2021 Nov 4;12:597907.doi: 10.3389/fphar.2021.597907. PMID: 34803661; PMCID: PMC8599800.
15. Savoldi A, Carrara E, Piddock LJV, Franceschi F, Ellis S, Chiamenti M, Bragantini D, Righi E, Tacconelli E. The role of combination therapy in the treatment of severe infections caused by carbapenem resistant gram- negatives: a systematic review of clinical studies. BMC Infect Dis. 2021 Jun 9;21(1):545.doi: 10.1186/s12879-021-06253-x. PMID: 34107899; PMCID: PMC8188907.
16. Giaccari LG, Pace MC, Passavanti MB, Gargano F, Aurilio C, Sansone P. Ceftolozane/Tazobactam for Resistant Drugs Pseudomonas aeruginosa Respiratory Infections: A Systematic Literature Review of the Real-World Evidence. Life (Basel). 2021 May 24;11(6):474. doi: 10.3390/life11060474. PMID: 34073847; PMCID: PMC8225018.
17. Soriano A, Carmeli Y, Omrani AS, Moore LSP, Tawadrous M, Irani P. Ceftazidime-Avibactam for the Treatment of Serious GramNegative Infections with Limited Treatment Options: A Systematic Literature Review. Infect Dis Ther. 2021 Dec;10(4):1989-2034. doi: 10.1007/s40121-021-00507-6. Epub 2021 Aug 11. PMID: 34379310; PMCID: PMC8355581.

Ward-level audit

Record ID

_____

Do you need the instructions on how to fill out the Audit and Feedback form?

◯ Yes
◯ No

INSTRUCTIONS FOR COMPLETING THE AUDIT AND FEEDBACK FORM

This initial form aims to collect preliminary information about the ward and the prescriptions that will be targeted during the audit. Before starting, you must decide what target prescriptions you will evaluate. The audit process can be either cross-sectional (i.e. the evaluation of the appropriateness of the antibiotic prescription at a specific time point) or longitudinal (i.e., the evaluation of part of the course /the entire course of a specific antibiotic). You will also need to select the time period for which you will evaluate the appropriateness of prescriptions (e.g. all patients receiving antibiotics on a given day, all target antibiotics prescribed in a given month, all positive blood cultures in a given month...).

Through this form, it will be possible to perform the following types of audits:

All prescriptions (cross-sectional audits) -> Evaluate the appropriateness of every prescription that is active at the time of the audit (can be up to five antibiotic molecules together); Surgical prophylaxis (cross-sectional) -> Evaluate all patients receiving surgical prophylaxis (SAP) at the time of the audit; (longitudinal) -> Evaluate the whole course of SAP for a given group of patients undergoing surgery (i.e., all patients operated in a week/month); Only selected (priority) antibiotic (broad spectrum, novel antibiotic - longitudinal)-> Evaluate the appropriateness of the use of the antibiotic longitudinally (can be prophylactic, empiric, targeted, or both); Only prescriptions lasting more than a given duration (e.g., 7 days - longitudinal) -> Evaluate the appropriateness of the molecules that are prescribed for over 7 days (can be prophylactic, empiric, targeted, or both); Only microbiologically documented UTIs or asymptomatic bacteriuria in a pre-defined time period -> Evaluate the empiric (if any) and the targeted therapy (if any) for the index urine culture (list 'no antibiotic' if the microbiological results were deemed as non-significant, also polymicrobial urine cultures can be considered); Only microbiologically documented BSIs in a pre-defined time period-> Evaluate the empiric and the targeted therapy administered for the index blood culture (include only the first clinically significant isolate per each patient). In the following form(s), you will enter individual-level patient data relative to the prescriptions that you are going to evaluate. It is important that you keep track of the time spent on the task because you will be asked to report this information at the end of the audit.

NB. According to the REVERSE protocol, your team should collect at least 20 patient-level assessments per ward (medicine and surgery) each month.

Audit date

_____
(Refers to the date on which you are performing the audit)

Audit timeframe START date

_____
(Refers to the date of the prescriptions that you are going to evaluate)

Audit timeframe END date

_____

In which REVERSE area are you performing the audit?

(Refers to the date of the prescriptions that you are going to evaluate. If you are evaluating all prescriptions occurring in a given day, start and end date can be the same)

- ◯ Medical
- ◯ Surgical
- ◯ Hemato-oncology
- ◯ ICU

(You can include more than one ward in the same area ONLY if you perform the same audit type in the same timeframe. If you include more than one ward, you might want to add a note to each patient to be able to retrieve the data at a latter stage.)

Ward name / code

_____

(For internal use, list the name or the code of the included ward(s))

What prescriptions are you going to evaluate?*

- ◯ All prescriptions (cross-sectional)
- ◯ Surgical prophylaxis (cross-sectional)
- ◯ Surgical prophylaxis (longitudinal)
- ◯ Only selected antibiotics (broad spectrum, novel antibiotic - longitudinal)
- ◯ Duration (longitudinal)
- ◯ Microbiologically documented urinary tract infections and asymptomatic bacteriuria (both empiric and targeted)
- ◯ Microbiologically documented bloodstream infections (both empiric and targeted)

(* Refer to the protocol or to the instructions above for the definitions)

Number of patients admitted

_____

Number of patients receiving antibiotics

_____

Prevalence of patients receiving antibiotic

_____

Patient-level prescription evaluation

PATIENT CODE

_____

(for internal use, PLEASE do not use identifiers (name, surname, dob))

Age (years)	_____
Sex	○ M ○ F ○ Other
Admission date	_____
Site of infection (proven or suspected)	☐ Central nervous system ☐ Lung ☐ Gastrointestinal ☐ Genito-urinary ☐ Skin and soft tissue ☐ Abdomen ☐ Bone ☐ Cardiovascular ☐ Bacteremia ☐ Unknown ☐ No infection (prophylaxis, colonization, asymptomatic bacteriuria...) ☐ Other
Were the microbiological samples taken appropriately?	○ Yes ○ Partly yes (i.e. only some samples were taken or samples were taken after the start of antibiotics) ○ No (relevant samples were not taken) ○ Samples were taken but the patient had no signs of infection ○ Not applicable (microbiological samples not needed)
Has an ID consultation been requested?	○ Not requested, not necessary ○ Not requested but useful/necessary* ○ Requested, indication NOT followed ○ Requested, indication FOLLOWED (* according to local practice)
Does the patient have any allergy?	☐ None known ☐ Penicillin ☐ Cephalosporins ☐ All beta-lactams ☐ Glycopepetides ☐ Cotrimoxazole ☐ Others

APPROPRIATENESS EVALUATION

For how many antibiotic molecules are you going to evaluate the appropriateness for the current patient?

- ◯ 0
- ◯ 1
- ◯ 2
- ◯ 3
- ◯ 4
- ◯ 5

Is it appropriate that the patient is not receiving any antibiotic according to microbiological and clinical data?

- ◯ Yes
- ◯ No

DEFINITIONS OF APPROPRIATENESS

APPROPRIATE: therapy follows local guidelines in terms of antibiotic choice, dose, route, and duration OR therapy that will cover the (likely) causative pathogen and there is not a narrower spectrum or a more appropriate antibiotic available, OR therapy follows the indication of the 'antibiotic expert' consultant.
ADEQUATE: Therapy is not the optimal choice, but it is a reasonable alternative to cover the (likely) causative agent regarding antibiotic choice, dosage, route, or duration.
INAPPROPRIATE: Therapy is an unreasonable choice to cover the (likely) causative pathogen (in terms of molecule and/or dosage and/or route and/or duration), including:

excessive spectrum (i.e. a 'Watch' antibiotic when an 'Access' antibiotic is recommended in the guidelines or reported as susceptible in the antibiogram) antibiotic is added as an unnecessary combination dosage is inadequately low or high / duration is too long there is a significant mismatch with the recommended route of administration (i.e., an antibiotic with poor oral bioavailability prescribed per os for a severe infection, intravenous vancomycin for C. diff….) there is a significant allergy mismatch (the patient is allergic to the prescribed antibiotic OR there are more appropriate alternatives for the patient's allergy).
NOT ASSESSABLE: Indication not documented and unable to be determined from the notes.

ANTIBIOTIC 1

Molecule _____
Route of administration _____
Start date _____
Duration (days) _____
Is there a written indication on the patient's chart? _____
Is approval by the antibiotic expert/ABS team needed for this prescription? _____
PRESCRIPTION TYPE _____
Is this antibiotic appropriate for surgical prophylaxis? _____ If inappropriate for surgical prophylaxis, specify why _____ Is this antibiotic appropriate for empirical therapy? _____

If inappropriate for empirical therapy, specify why _____
Is this antibiotic appropriate as targeted therapy? _____
If inappropriate for targeted therapy, specify why _____
Is it appropriate that the patient is receiving this antibiotic as medical prophylaxis? _____

ANTIBIOTIC 2

Molecule _____
Route of administration _____
Start date _____
Duration (days) _____
Is there a written indication on the patient's chart? _____
Is approval by the antibiotic expert/ABS team needed for this prescription? _____

PRESCRIPTION TYPE _____
Is this antibiotic appropriate for surgical prophylaxis? _____ If inappropriate for surgical prophylaxis, specify why _____ Is this antibiotic appropriate for empirical therapy?

_____

If inappropriate for empirical therapy, specify why _____
Is this antibiotic appropriate as targeted therapy? _____
If inappropriate for targeted therapy, specify why _____
Is it appropriate that the patient is receiving this antibiotic as medical prophylaxis? _____

ANTIBIOTIC 3

Molecule _____
Route of administration _____
Start date _____
Duration (days) _____
Is there a written indication on the patient's chart? _____
Is approval by the antibiotic expert/ABS team needed for this prescription? _____
PRESCRIPTION TYPE _____
Is this antibiotic appropriate for surgical prophylaxis? _____ If inappropriate for surgical prophylaxis, specify why _____ Is this antibiotic appropriate for empirical therapy?

_____

If inappropriate for empirical therapy, specify why _____
Is this antibiotic appropriate as targeted therapy? _____
If inappropriate for targeted therapy, specify why _____
Is it appropriate that the patient is receiving this antibiotic as medical prophylaxis? _____

ANTIBIOTIC 4

Molecule _____

Route of administration _____
Start date _____
Duration (days) _____
Is there a written indication on the patient's chart? _____
Is approval by the antibiotic expert/ABS team needed for this prescription? _____
PRESCRIPTION TYPE _____
Is this antibiotic appropriate for surgical prophylaxis? _____ If inappropriate for surgical prophylaxis, specify why _____ Is this antibiotic appropriate for empirical therapy?

_____

If inappropriate for empirical therapy, specify why _____
Is this antibiotic appropriate as targeted therapy? _____
If inappropriate for targeted therapy, specify why _____

Is it appropriate that the patient is receiving this antibiotic as medical prophylaxis? _____

ANTIBIOTIC 5

Molecule _____

Route of administration _____
Start date _____
Duration (days) _____
Is there a written indication on the patient's chart? _____
Is approval by the antibiotic expert/ABS team needed for this prescription? _____
PRESCRIPTION TYPE _____
Is this antibiotic appropriate for surgical prophylaxis? _____ If inappropriate for surgical prophylaxis, specify why _____ Is this antibiotic appropriate for empirical therapy?

_____

If inappropriate for empirical therapy, specify why _____
Is this antibiotic appropriate as targeted therapy? _____
If inappropriate for targeted therapy, specify why _____
Is it appropriate that the patient is receiving this antibiotic as medical prophylaxis? _____

INSTRUCTIONS ON HOW TO COMPLETE / PROCEED

Once you have completed the patient-level audit form, you can save your work at the end as follows:

_____

Once you have completed the individual evaluation, mark it as 'completed' and use the 'Save & Add New Instance' button to open a new form for the next patient. Once you have completed the audit session and included all the patients, mark the last patient as 'complete' and 'Save & go to the next record' to finalize the audit data collection. If you wish to interrupt and return later, select 'Save & exit record'. Please, note that you will have to come back to this session later to complete the patient-level data collection and finalize the last form. If you wish to initiate a new audit session and change the audit target, area, or timeframe, you must complete/exit this record and 'Create a new record'. You can add here notes on the patient/audit session in the box (do not use identifiers such as name, surname, or date of birth).

Antibiotic rounds (ward-level data)

Antibiotic round date

_____

In which REVERSE area did you perform the antibiotic round?

- ○ Medical
- ○ Surgical
- ○ Hemato-oncology
- ○ ICU

(NB The REVERSE Protocol suggests this ABS element for high risks area such as ICU and Onco-hematology)

Ward name / code

_____

(For internal use, you can insert the name of the ward or the code)

Number of patients admitted in the ward

_____

Number of patients receiving antibiotics

_____

Number of patients receiving appropriate antibiotics

_____

Number of modifications discussed/suggested

_____

Number of modifications accepted

_____

Additional notes

_____

Time spent on the task

How much time (IN MINUTES) did it take to perform the antibiotic round?

_____

How much time (IN MINUTES) did it take to perform the audit (without considering breaks/interruptions)?

_____

How many treatment modifications were suggested? (only for cross-sectional audits with feedback)

_____

How many treatment modifications were accepted in the 48-72 hours following the audit and feedback process?

_____

Additional notes

_____

ABS team and process indicators (quarterly data)

In what REVERSE area were you able to perform ABS activities according to the REVERSE protocol for this trimester?	☐ General Medicine ☐ Surgery ☐ Intensive-care ☐ Hemato-oncology (Select only the area for which some modification according to the baseline ABS existing activities were introduced following the REVERSE ABS protocol)
Who is participating in REVERSE ABS activities for the current trimester?	☐ ID physician(s) ☐ Other clinician(s) with expertise in antibiotic prescribing ☐ Ward doctor(s) ☐ Pharmacist(s) ☐ Microbiologist(s) ☐ IT expert(s) ☐ Nurse(s) ☐ Other professional(s) ☐ No changes in the personnel compare to the previous trimester* (*do not select this if it is the first trimester!)
How many Full-Time-Equivalents (FTEs) of the ID PHYSICIAN working time are dedicated to ABS?	_____ (1 FTE: 1 professional working 100% on ABS)
How many Full-Time-Equivalents (FTEs) of the 'OTHER CLINICIAN' working time are dedicated to ABS?	_____ (1 FTE: 1 professional working 100% on ABS)
How many Full-Time-Equivalents (FTEs) of the 'WARD PHYSICIAN' working time are dedicated to ABS?	_____ (1 FTE: 1 professional working 100% on ABS)
How many Full-Time-Equivalents (FTEs) of the PHARMACIST working time are dedicated to ABS?	_____ (1 FTE: 1 professional working 100% on ABS)
How many Full-Time-Equivalents (FTEs) of the MICROBIOLOGIST working time are dedicated to ABS?	_____ (1 FTE: 1 professional working 100% on ABS)
How many Full-Time-Equivalents (FTEs) of the IT EXPERT working time are dedicated to ABS?	_____ (1 FTE: 1 professional working 100% on ABS)

How many Full-Time-Equivalents (FTEs) of the NURSE working time are dedicated to ABS?

_____

(1 FTE: 1 professional working 100% on ABS)

How many full-time equivalents (FTEs) of the OTHER PROFESSIONAL working time are dedicated to ABS?

_____

(1 FTE: 1 professional working 100% on ABS)

please specify the expertise

_____

INTERNAL MEDICINE

Patient days (quarterly) _____

Overall quarterly DOTs (whole ATCJ01, crude) _____

Overall quarterly DDDs (whole ATCJ01, in grams) _____

LIST THE 10 ANTIBIOTIC OF MOST FREQUENT USE DOTs (crude, quarterly) DDDs (in grams, quarterly)

_____ _____ _____
_____ _____ _____
_____ _____ _____
_____ _____ _____
_____ _____ _____
_____ _____ _____
_____ _____ _____
_____ _____ _____
_____ _____ _____
_____ _____ _____

SURGERY

Patient days (quarterly) _____

Overall quarterly DOTs (crude, whole ATCJ01) _____

Overall quarterly DDDs (in grams, whole ATCJ01) _____

LIST THE 10 ANTIBIOTIC OF MOST FREQUENT USE DOTs (crude, quarterly) DDDs (in grams, quarterly)

_____ _____ _____
_____ _____ _____
_____ _____ _____
_____ _____ _____
_____ _____ _____
_____ _____ _____
_____ _____ _____
_____ _____ _____
_____ _____ _____
_____ _____ _____

ICU

Patient days (quarterly) _____

Overall quarterly DOTs (crude, whole ATCJ01) _____

Overall quarterly DDDs (in grams, whole ATCJ01) _____

LIST THE 10 ANTIBIOTIC OF MOST FREQUENT USE DOTs (crude, quarterly) DDDs (in grams, quarterly)

_____ _____ _____
_____ _____ _____
_____ _____ _____
_____ _____ _____
_____ _____ _____
_____ _____ _____
_____ _____ _____
_____ _____ _____
_____ _____ _____
_____ _____ _____

HEMATO-ONCOLOGY

Patient days (quarterly) _____

Overall quarterly DOTs (crude, whole ATCJ01) _____

Overall quarterly DDDs (in grams, whole ATCJ01) _____

LIST THE 10 ANTIBIOTIC OF MOST FREQUENT USE DOTs (crude, quarterly) DDDs (in grams, quarterly)

_____ _____ _____
_____ _____ _____
_____ _____ _____
_____ _____ _____
_____ _____ _____
_____ _____ _____
_____ _____ _____
_____ _____ _____
_____ _____ _____
_____ _____ _____

Notes

_____

Supplementary Section 2

Point Prevalence Surveys

CRO screening:

All patients hospitalised in intensive care, haematology-oncology, general surgery, and internal medicine (general internal medicine and subspecialty wards including infectious diseases) in the REVERSE hospitals will be eligible for CRE, CRAB, and CRPA screening by rectal swab. However, only 250 patients (200 patients with length of stay 3 days or more; 50 patients with length of stay 1-2 days) will be screened. The duration of hospital stay on the day of the survey is recorded. These swabs will be performed in addition to any routine, hospital level surveillance swabs.

The centralized REVERSE laboratory (UMCU) will provide the included hospitals with transwabs containing liquid Amies for sampling and all necessary medical packing for international shipping of biological samples in order to reach the UMCU for testing. Swabs will be stored at room temperature (RT) before use. After the swab, samples will be stored at 4C and shipped at RT to the Central REVERSE laboratory (UMCU), within two weeks of sampling. Sampling and shipping will be done within the month scheduled for screening.

The swabs will be processed at a centralized REVERSE laboratory (UMCU) and results will not be identifiable on a patient level. When more than 250 swabs are received from a single survey, the Central REVERSE lab (UMCU) will take a weighted sample of 200 patients with a length of stay of 3 days or more. The remaining 50 will be a random sample of the patients with a length of stay with a maximum of 2 days. A total of 250 swabs will be included per time point per centre.

Sampling will be performed at three time points: before the IPC intervention, before the ABS intervention and at the end of the intervention period. See the schedule included in Appendix 1.

Whole genome sequencing

The swabs are cultured using selective agarplates. Growth of colonies suspected for *Enterobaceriaceae*, *P. aeruginosa* or *A. baumanii* will be further processed using mass spectrophotometry and a phenotypic susceptibility test. Phenotypically confirmed CRE isolates stored at -80°C are plated onto blood agar, incubated overnight at 37°C and checked for purity. One colony is used to inoculate 3 mL LB followed by overnight incubation at 37°C. The bacteria in 1.6 mL suspension are pelleted in an Eppendorf tube. The fluid is decanted and after a brief spin the remaining fluid is removed by using a pipette. The pellet is suspended in 300 µl microbead solution, which is subjected to DNA extraction with the Ultraclean Microbial DNA isolation kit (Mo Bio Laboratories, Carlsbad, CA, USA). The DNA concentration is measured using the Qubit double-stranded DNA (dsDNA) BR assay kit (Life Technologies, Carlsbad, CA, USA) or picogreen. One nanogram of bacterial DNA is used for library preparation. The DNA library is prepared using the Nextera XT library preparation kit with the Nextera XT v2 index kit (Illumina, San Diego, CA, USA). Subsequently, the library is sequenced on either a MiSeq sequencer, using the MiSeq reagent kit v2 generating 250-bp paired-end reads, or on a NextSeq with 2x 150 bp paired-end reads (Illumina, San Diego, CA, USA). Sequencing is aimed at a coverage of at least 50-fold. MiSeq data are processed with MiSeq control software

v2.4.0.4 and MiSeq Reporter v2.4 and HiSeq data with bcl2fastq2 conversion software v1.8.4 (Illumina, San Diego, CA, USA). Bioinformatics analyses are performed with the snakemake pipeline bactofidia, release Coniophis. It includes quality check with FastQC (version 0.11.9) and trimming and adaptor removal with trim-galore (version 0.6.2) with a phred score cut-off of 20. *De novo* assembly is performed with SPAdes version 3.11.1 with a k-mer range of 57,97,127 for miseq data and 37,57,77 for hiseq data. Contigs with a length smaller than 500 basepairs or a k-mer coverage of less than 10 are excluded from further analysis to remove low-level contamination. For each assembled genome, the number of scaffolds, the N50, the maximum scaffold length, and the percentage of the expected genome size are determined with Quast and coverage of each contig and mean depth is determined with bbmap2 version 37.62. WGS-based species identification and MLST typing is done by scanning contigs against the whole PubMLST database with [mlst](http://bioconda.github.io/recipes/mlst/README.html), version 2.16.2. Resistance gene determination is performed with abricate version 0.8 using the resfinder database, downloaded on 2019-Apr-23. Potential target genes need to show a minimum DNA identity of 90%. All quality parameters are visualized in a summarizing report with multiqc, version 1.6a0.

Assembled genomes should have a coverage of at least 20x, contain less than 600 contigs and the genome size should be within the range reported for the species.

WGS-based typing

The MLST target definer function of Ridom SeqSphere (Ridom, Münster, Germany) is used to define target gene sets for all species with at least 10 isolates available. Depending on the number of available complete reference genomes, typing schemes are developed at the genus level (*Citrobacter* spp.), genetic-complex level (*E. cloacae* complex), or species level (*E. coli*, *K. oxy- toca*, and *K. pneumoniae*). For each scheme, one annotated and publicly available complete genome (chromosome) is used as a reference genome. For *K. pneumoniae* and *E. coli* schemes are available.

New schemes will be developed based on a reference genome, preferably of the type strain or a complete circular genome. Additional genomes are selected to define the gene set. These additional genes should be from well-defined isolates and of high quality. Repeat isolates should be avoided.

Of those, genes that are present in all query genomes with a sequence identity of at least 90% and an alignment of 100% are classified as core genome targets; the remaining genes are classified as accessory genome targets. wgMLST schemes include all whole-genome targets; core genome MLST (cgMLST) schemes include only the core genome targets.
All-to-all distance matrices, describing pairwise genetic distances, are constructed separately for core, accessory, and whole-genome target gene sets. The pairwise genetic distance is defined as the proportion of allele differences and is calculated by dividing the number of allele differences by the total number of good targets shared by both sequences, i.e., pairwise ignoring missing values.

Clonal relatedness will be based on the genetic distance and cut offs as defined previously based on a combination of epidemiological and molecular data in a similar setting [4].

Default SeqSphere settings are used for the development of schemes and the analysis of sequences. Samples that deviate more than 10% from the others are removed for generating a Neighbour Joining Tree and missing values are an own category.

A detail protocol is available at the UMCU under document name: Assessing relatedness between bacteria of the same species using NGS data and Ridom SeqSphere+. Document number: BAC-wi-071.

Hai Surveillance Ecdc

Record ID

_____

Date data was collected

_____

Patient Information:

Demographics

Devices

Ward: _____

Admission date and time: _____

Age: _____

Sex: _____

Central venous catheter present:

_____

Peripheral venous catheter present:

_____

Urinary catheter present:

_____

Is the patient intubated?

_____

Was this patient admitted to ICU during this admission?

◯ Yes
◯ No

How many times was this patient admitted to ICU?

_____

(If the patient was admitted to the ICU - that would be 1 ICU admission. If the patient was admitted to the ward and transferred to ICU, that is also 1 ICU admission. If the patient was admitted to ICU, discharged, then transferred back, that would be 2 ICU admissions.)

Surgery since admission?

◯ No surgery
◯ Minimally invasive surgery/ non-NHSN surgery
◯ NHSN surgery
◯ Unknown

If NHSN surgery, please specify

_____

McCabe score	◯ Non-fatal disease ◯ Ultimately fatal disease ◯ Rapidly fatal disease ◯ Unknown

Antimicrobial Information

Was the patient on antimicrobials at the time or before the sample was sent?	◯ Yes ◯ No

Select antimicrobial(s) that the patient received when the sample was sent

if selecting other: please only enter antibacterial agents and NOT antivirals or antifungals

- ☐ amikacin
- ☐ amoxicillin-clavulanic acid
- ☐ ampicillin
- ☐ ampicillin/sulbactam
- ☐ azithromycin
- ☐ aztreonam
- ☐ cefazolin
- ☐ cefepime
- ☐ cefiderocol
- ☐ cefotaxime
- ☐ cefoxitin
- ☐ ceftaroline
- ☐ ceftazidime
- ☐ ceftazidime/avibactam
- ☐ ceftobiprole
- ☐ ceftolozane-tazobactam
- ☐ ceftriaxone
- ☐ cefuroxime
- ☐ ciprofloxacin
- ☐ clarithromycin
- ☐ clindamycin
- ☐ colistin
- ☐ dalbavancin
- ☐ daptomycin
- ☐ doxycycline
- ☐ ertapenem
- ☐ eravacycline
- ☐ fosfomycin
- ☐ gentamicin
- ☐ imipenem
- ☐ imipenem-relebactam
- ☐ levofloxacin
- ☐ linezolid
- ☐ meropenem
- ☐ meropenem-varbobactam
- ☐ moxifloxacin
- ☐ nitrofurantoin
- ☐ oxacillin
- ☐ penicillin
- ☐ piperacillin
- ☐ piperacillin/tazobactam
- ☐ rifampicin
- ☐ teicoplanin
- ☐ tigecycline
- ☐ tobramycin
- ☐ trimethoprim-sulfamethoxazole
- ☐ vancomycin
- ☐ metronidazole
- ☐ other
- ☐ none

( )

If other, please specify

only anti-bacterials

_____

Please specific route of antimicrobial administration (check all that apply)

- ☐ parentral
- ☐ oral
- ☐ rectal
- ☐ inhaled

Were the antimicrobials changed or started after the sample report/ susceptibilities were available?

Include antimicrobials changes up to 2 days after the report was available.

- ◯ Yes
- ◯ No

Select antimicrobial(s) after change

if selecting other: please only enter antibacterial agents and NOT antivirals or antifungals

- ☐ amikacin
- ☐ amoxicillin-clavulanic acid
- ☐ ampicillin
- ☐ ampicillin/sulbactam
- ☐ azithromycin
- ☐ aztreonam
- ☐ cefazolin
- ☐ cefepime
- ☐ cefiderocol
- ☐ cefotaxime
- ☐ cefoxitin
- ☐ ceftaroline
- ☐ ceftazidime
- ☐ ceftazidime/avibactam
- ☐ ceftobiprole
- ☐ ceftolozane-tazobactam
- ☐ ceftriaxone
- ☐ cefuroxime
- ☐ ciprofloxacin
- ☐ clarithromycin
- ☐ clindamycin
- ☐ colistin
- ☐ dalbavancin
- ☐ daptomycin
- ☐ doxycycline
- ☐ ertapenem
- ☐ eravacycline
- ☐ fosfomycin
- ☐ gentamicin
- ☐ imipenem
- ☐ imipenem-relebactam
- ☐ levofloxacin
- ☐ linezolid
- ☐ meropenem
- ☐ meropenem-varbobactam
- ☐ moxifloxacin
- ☐ nitrofurantoin
- ☐ oxacillin
- ☐ penicillin
- ☐ piperacillin
- ☐ piperacillin/tazobactam
- ☐ rifampicin
- ☐ teicoplanin
- ☐ tigecycline
- ☐ tobramycin
- ☐ trimethoprim-sulfamethoxazole
- ☐ vancomycin
- ☐ metronidazole
- ☐ other
- ☐ none

( )

If other, please specify

only antibacterials

_____

Please specific route of antimicrobial administration (check all that apply)

- ☐ parentral
- ☐ oral
- ☐ rectal
- ☐ inhaled

HAI Information

Date of onset: _____

diagnosis: _____

if surgical site infection, please select type:

_____

If pneumonia, please select type:

_____

If urinary tract infection, please select type:

_____

if bloodstream infection, please select type:

_____

_____

if other, please specify: _____

If catheter related infection, please specify type:

_____

Please indicate if the patient had a device in the 48h prior (for BSI and PN) or in the 7d prior (for UTI) to onset of infection

relevant device present (for UTIs, BSIs, and PNs)? _____

infection present on admission? _____

origin of infection: _____

associated with current ward? _____

Organism isolated: _____

Additional organisms isolated? _____

Organism isolated: _____

Additional organisms isolated? _____

Organism isolated: _____

Please specify species if applicable:

Organism 1:

_____

_____

Organism 2:

_____

_____

Organism 3:

_____

_____

Supplementary Section 4

Hospital administrative data variables

- Hospital number
- Quarter
- Total number of beds in the hospital, in REVERSE ICU, internal medicine, surgery, hematology-oncology, and transplant wards
- Patient days in entire hospital, REVERSE ICU, internal medicine, surgery, hematology-oncology, and transplant wards
- Number of patients on isolation on the 1st of the month at 00:00 (entire hospital and REVERSE wards)
- Average length of stay (entire hospital, last 3 months)
- Admissions over the last 3 months (entire hospital and REVERSE wards)
- Mean admission age (entire hospital and REVERSE wards)
- Standard deviation admission age (entire hospital and REVERSE wards)
- Median admission age (entire hospital and REVERSE wards)
- IQR admission age (entire hospital and REVERSE wards)
- Readmissions(entire hospital and REVERSE wards)
- Proportion of admissions that are male (entire hospital and REVERSE wards)
- Number of blood cultures done (entire hospital)
- Number of. C diff tests done (entire hospital)
- Litres of alcohol based hand rub used (entire hospital)
- Litres of alcohol based hand rub used (REVERSE wards)
- In hospital mortality

Supplementary section 5

Antimicrobial data collected

Data was collected separately for whole hospital and REVERSE wards

Variables collected quarterly for antimicrobial use during the REVERSE project

Hospital ID	Fosfomycin PO
Quarter	Gentamicin
Amikacin	Imipenem
Amoxicillin IV	Imipenem-relebactam
Amoxicillin PO	Levofloxacin (total)
Amoxicillin-clavulanic acid IV	Levofloxacin IV
Amoxicillin-clavulanic acid PO	Levofloxacin PO
Ampicillin IV	Linezolid (total)
Ampicillin PO	Linezolid IV
Ampicillin-sulbactam	Linezolid PO
Azithromycin IV	Meropenem
Azithromycin PO	Meropenem-vaborbactam
Cefazolin	Metronidazole (total)
Cefepime	Metronidazole IV
Cefiderocol	Metronidazole PO
Cefotaxime	Moxifloxacin (total)
Ceftazidime	Moxifloxacin IV
Ceftazidime-avibactam	Moxifloxacin PO
Ceftolozane-tazobactam	Oxacillin (total)
Ceftriaxone	Oxacillin IV
Ciprofloxacin IV	Oxacillin PO
Ciprofloxacin PO	Penicillin
Clarithromycin IV	Piperacillin
Clarithromycin PO	Piperacillin-tazobactam

Clindamycin IV	Tedizolid (total)
Clindamycin PO	Tedizolid IV
Colistin	Tedizolid PO
Dalbavancin	Tigecycline
Daptomycin	Tobramycin
Doxycycline (total)	Trimethoprim-sulfamethoxazole (total)
Doxycycline IV	Trimethoprim-sulfamethoxazole IV
Doxycycline PO	Trimethoprim-sulfamethoxazole PO
Ertapenem	Vancomycin
Fosfomycin IV	ATC J01 DDD



Research and Innovation Action
H2020-SC-1-2020-Single-Stage-RTD

Standard Operating Procedure (SOP) – Dataset Pseudonymization in Excel

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Purpose

The purpose of this document is to pseudonymize the dataset collected using the REDCap tool "HAI Surveillance ECDC" within the REVERSE project, developed in accordance with ECDC protocol v.5.3.

Variables that require modification are:

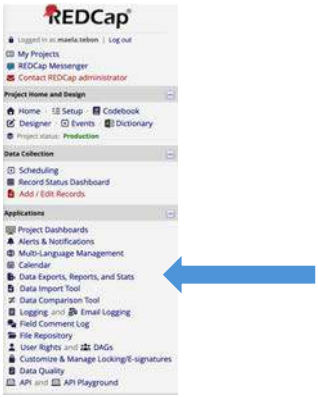
1) Age (currently stored as an integer), to be converted into predefined categorical ranges.
2) Date and time of admission [adm_date] and Date of infection onset [onset_date], which shall be replaced with a single variable reporting the difference in calendar days between the two.

Before exporting the dataset, verify in REDCap that all relevant instances have been completed.

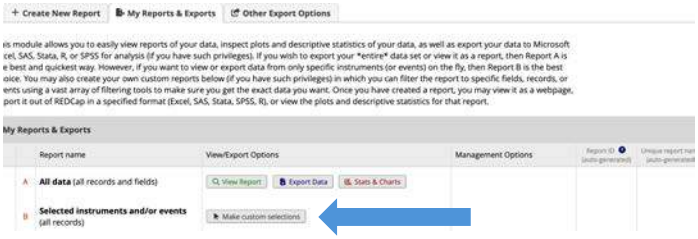
Data Export from REDCap

Objective: To extract the dataset from REDCap in a standardized format.

1. Log in to REDCap using your institutional credentials and select the instrument.
2. From the left-hand menu, select "Data Exports, Reports, and Stats".



3. Under the "My reports & Exports" section, select "Make custom selection".



4. In the "Instruments" section, select the form corresponding to HAI Surveillance ECDC (a).
5. Include all events from March 2022 to March 2026 for IT1, IT3, IT4, IT5, and IT6, and to June 2026 for IT2 (b). Ensure that all events are selected by reviewing the full list, including those not immediately visible on screen (scroll down if necessary).

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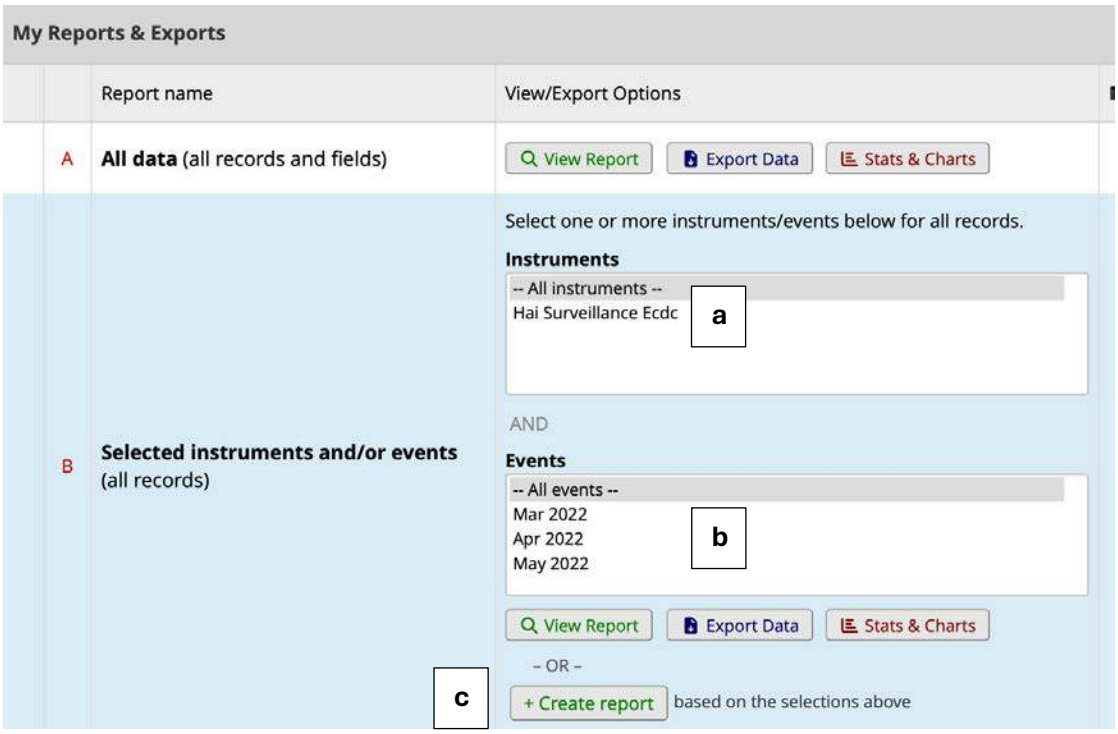
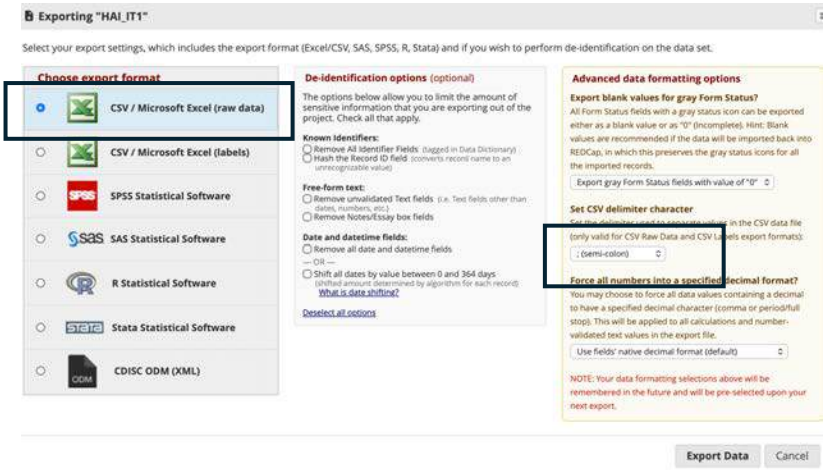
6. Select “+ Create report” (c) and assign the name “HAI_hospitalcode” and click on “Save report”.



7. From the “My report & Exports” section, select the report and click “Export Data”, choosing CSV / Microsoft Excel (raw data) as the export format. In the “Advanced data formatting options”, set the CSV delimiter to semicolon (;), as shown below.



8. Download the file by clicking on the icon: 

9. Save the exported file using the naming convention “HAI_hospitalcode.xlsx”. If the file is downloaded as a CSV, save it as an Excel workbook (.xlsx) before proceeding.

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Pre-processing

The exported file may contain a blank row immediately below the header row. If present, this row must be deleted before applying any formulas.

Perform pseudonymization on a separate copy named: HAI_hospitalcode_pseudoanonymised.

Review the dataset and identify rows corresponding to instances that were opened but never completed. Before removing any such rows, verify in REDCap that they contain no recorded data (i.e., all fields are empty across the instance). Do not remove rows containing valid data. If rows are removed, document the removed instances (event and instance number) to ensure traceability.

Before starting, it is recommended to hide all columns from J to EI to simplify the workspace and avoid accidental modifications.

ALERTS

1. Excel may use either semicolon (;) or comma (,) as a function separator. This SOP shows formulas with semicolons. If your Excel expects commas, replace ";" with "," in the formulas.
2. Formulas are provided in both English (EN) and Italian (IT) to accommodate different Excel language settings. Use the version corresponding to your local Excel configuration.

Creation of "patient group" variable

Objective: To create a non-identifiable variable allowing grouping of multiple infections belonging to the same patient.

1) At the end of the sheet, insert a new column named: temp_key
2) In the second row, insert =F2&"|"&G2&"|"&H2&"|"&I2&"|"&B2
3) Press Enter, then double-click the fill handle (bottom-right) to copy the formula down. Ensure that the formula is applied to all rows in the dataset before proceeding.
4) Insert a new column named "patient_group_id".
5) In the second row, insert:
   EN: =MATCH(EX2;$EX$2:$EX$100000;0)
   IT: =CONFRONTA(EX2;$EX$2:$EX$100000;0)
6) Copy the formula down. This assigns the same numeric identifier to identical keys. Ensure that the formula is applied to all rows in the dataset before proceeding.
7) Fix the results: select the entire "patient_group_id" column, Copy, Paste Special, Values, and Enter.
8) Delete the "temp_key" column.

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Age categorisation

Objective: Replace numeric ages with categorical ranges.
ALERT: The cell reference used in the formula* (H2) corresponds to the "age" column in the data set. The column letter depends on the location of the new "age_range" column. Before applying the formula, check which column contains the "age" values and adjust the reference accordingly, if needed.

1) Ensure the "age" values are numeric: Select the entire "age" column, then go to Data → Text to Columns, keep the default Delimited option (the "Tab" checkbox can remain selected), click Next → Next → Finish. This converts "numbers stored as text" into true numeric values.
2) Insert a new column named "age_range".
3) Before typing the formula, make sure the "age_range" column format is set to General. Home → Number Format → General.
4) In the second row, insert:
   EN: `=IF(ISNUMBER(H2);IF(H2<18;"<18";IF(H2>90;">90";FLOOR(H2;5)&"-"&FLOOR(H2;5)+4));"NA")`
   IT:
   `=SE(VAL.NUMERO(H2);SE(H2<18;"<18";SE(H2>90;">90";ARROTONDA.DIFETTO(H2;5)&"-"&ARROTONDA.DIFETTO(H2;5)+4));"NA")`.
5) Press Enter, then double-click the fill handle (bottom-right) to copy the formula down. Ensure that the formula is applied to all rows in the dataset before proceeding.
6) Fix the results: select the entire "age_range" column, Copy, Paste Special, Values, and Enter.
7) Check several records for consistency between "age" and "age_range".
8) Replace **all values** in the "age" column (excluding the header) with "NA", ensuring that all cells are overwritten.

Days between admission and infection onset

Objective: Replace the "Date and time of admission" [adm_date] and the "Date of infection onset" [onset_date] with a single numeric variable reporting calendar day between the two.
ALERT: The cell references in the formula (e.g., "G2" for adm_date and "EJ2" for onset_date) may vary depending on the file structure.
Before applying the formula, identify which columns contain these variables and update the references accordingly.

1) Select the entire "adm_date" column, then go to Data → Text to Columns, click Next → Select Date and choose the format corresponding to the data format displayed in the exported file:
   YMD (in Italian: AMG) for dates displayed as YYYY-MM-DD
   DMY (in Italian GMA) for dates displayed as DD/MM/YYYY
   → Finish. This ensures that date and time values are correctly recognized as valid Excel data/time values.

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2) Use the same procedure with the “onset_date” column.
3) Check several records for consistency.
4) Insert a new column named “days_onset” and set the column format to Number (integer) to ensure numeric values are correctly stored.
5) In the second row, insert:
   EN: =IF(AND(ISNUMBER(EJ2);ISNUMBER(G2));INT(EJ2)-INT(G2);"null")
   IT: =SE(E(VAL.NUMERO(EJ2);VAL.NUMERO(G2));INT(EJ2)-INT(G2);"null")
6) Press Enter, then double-click the fill handle to copy the formula down.
   Ensure that the formula is applied to all rows in the dataset before proceeding.
7) Fix the results: select the entire column, Copy, Paste Special, Values, and Enter.
8) Replace all values in the “adm_date” and “onset_date” columns (excluding the header) with “NA”, ensuring that all cells are overwritten.

Data check

The following data quality checks are strongly recommended:

- Review records with instance **≤ 2** to confirm that cases meet HAI case definition criteria (e.g., patients potentially admitted from another hospital; symptoms occurring within 30 days of a surgical intervention).
- Investigate records with negative *days_onset* values by verifying admission and onset dates; if necessary, reassign instances to the appropriate event.
- Review records with *days_onset* > 100 to identify potential inconsistencies.
- Ensure that the number of HAI cases reported in the overall (hospital data) file, stratified by quarter, matches the number of HAI cases recorded in the final Excel dataset submitted to the coordinator.

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Supplementary Section 7

IPC Score

To assess the level of uptake for each IPC component, we used a semi-quantitative scoring system that captured three dimensions:

- Degree of activity (measured as ward-quarters or quarters),
- Effort (intensity of activities such as audits or observations), and
- Performance (observed compliance or outcomes).

Each dimension was categorized into three levels (low, moderate, high) using predefined thresholds tailored to each component. A detailed breakdown is presented in Table 5.

Table 1: Semi-Quantitative Scoring Criteria for IPC Bundle Components: Degree of Activity, Effort and Performance

	Hand hygiene (HH)		Contact precautions (CP)		Active surveillance (AS)		Isolation & Cohorting (I&C)		Environmental hygiene (EH)		Outbreak investigation (OI)	
Degree of activity (time and place)	ward-quarters	≤50%	ward-quarters	≤50%	ward-quarters	≤50%	ward-quarters	≤50%	ward-quarters	≤50%	quarters	1
		50%<X≤75 %		50%<X ≤75%		50%<X ≤75%		50%<X ≤75%		50%<X≤ 75%		2
		>75%		>75%		>75%		>75%		>75%		3 or 4
Effort	HH observations	≤ 2.5 per ward per quarter	achieved audits (%quarters)	≤50%	No of MDRO under effort	1	achieved audits (%quarters	≤50%	tools to assess cleaning	Visual inspection		
		2.5<X≤3.5 per ward per quarter		50%<X ≤75%		2		50%<X ≤75%		ATP or Fluorescent gel		
		>3.5 per ward per quarter		>75%		3		>75%		Microbiological cultures		
Performance	HH compliance	≤50%	compliance_ patients (%)	≤50%			time to I/C	>48h				
		50%<X≤75 %		50%<X ≤75%				24-48h				
		>75%		>75%				<24h				
			Infrastructure compliance (%)	≤50%								
				50%<X ≤75%								
				>75%								
Maximum possible score	9		12		6		9		6		3	

Legend:

Low level (1 point)

Medium level (2 points)

High level (3 points)