



OPTIMISING SKIN ANTISEPSIS

FOR AN ENHANCED PREVENTION
OF HEALTHCARE-ASSOCIATED INFECTIONS
IN THE EU

EUROPEAN POLICY RECOMMENDATIONS

CONTENT

| | |
|---|----|
| I. FOREWORD | 4 |
| II. EXECUTIVE SUMMARY | 6 |
| III. PATIENT SAFETY AND HEALTHCARE-ACQUIRED INFECTIONS - RELEVANT CONTEXT IN THE EU | 8 |
| A. POLITICAL BACKGROUND | 9 |
| B. SURGICAL SITE INFECTIONS AND CATHETER-RELATED BLOODSTREAM INFECTIONS, A CLINICAL THREAT | 12 |
| C. CONTAMINATION OF BLOOD CULTURES, A PRECLINICAL CHALLENGE AND CONTRIBUTING FACTOR TO AMR | 13 |
| IV. WHY IS SKIN ANTISEPSIS CRITICAL | 14 |
| V. MEDICINAL PRODUCTS OR BIOCIDES? A REGULATORY ISSUE | 16 |
| VI. OPTIMISING SKIN ANTISEPSIS TO PREVENT INFECTIONS | 20 |
| VII. PREVENTING ADVERSE EVENTS IN SKIN ANTISEPSIS: “IT’S NOT ONLY WHAT YOU USE, IT’S THE WAY YOU USE IT” | 26 |
| VIII. OVERVIEW OF RECOMMENDATIONS | 31 |
| CONTRIBUTORS | 33 |
| REFERENCES | 35 |

I. FOREWORD

DEAR READERS,

It is clearly true that patient safety, a key factor to overall healthcare quality, and the prevention of Healthcare-Associated Infections as a threat to patient safety have been a cornerstone of EU and national healthcare policies for years. However, we believe that much remains to be done with regard to the prevention of Healthcare-Associated Infections (HAIs), universally relevant to patients at every single health-care encounter and which demands comprehensive solutions. Skin antiseptics has certainly a role to play in this regard.

We hereby would like to recall that, as stressed by this Parliament, high-quality healthcare is recognised as a fundamental right by the EU. We are convinced that a harmonised approach across EU Member States in skin antiseptics can significantly contribute to optimising the prevention of HAIs and ensuring a consistent level of patient safety in all countries.

The institution we represent urged the Commission to foster the exchange of information on initiatives concerned with patient safety and quality of care. We welcome this white paper as an example of an exchange of knowledge and best practices between a group of pan-European experts that can translate into increased safety for all European patients. We also applaud the fact antimicrobial resistance is one the topics addressed in the paper, for we consider that this is a serious and growing threat to patient safety that needs to be considered in the frame of any initiative on the prevention of HAI.

As Members of the European Parliament, we are committed to ensuring that all citizens have equal access to health care with the highest possible quality and safety. It is our hope that the information, expertise and policy recommendations contained within this paper will be acted upon by policy makers at European and national level. We prompt the Commission and relevant institutions to effectively implement these recommendations so that all European patients have access to the same and highest standard of safe and quality healthcare.*

* European Parliament. 2013. "Report on the report from the Commission to the Council on the basis of Member States' reports on the implementation of the Council Recommendation (2009/C 151/01) on patient safety, including the prevention and control of healthcare-associated infections (2013/2022(INI))". 4 October 2013. Available at: <http://www.europarl.europa.eu/sides/getDoc.do?pubRef=-//EP//TEXT+REPORT+A7-2013-0320+0+DOC+XML+V0//EN>

II. EXECUTIVE SUMMARY

While the European Union has seen significant developments in patient safety in the last decade and all countries have developed specific policies on patient safety or embedded them as priorities in their healthcare policies, not all countries have implemented specific measures to prevent Healthcare-Associated Infections (HAIs), i.e., the range of infections acquired in hospitals or as a result of healthcare interventions.

That explains that, whereas at least 20% of HAIs are estimated to be preventable, these remain a significant risk to patients and a heavy burden on healthcare systems. Aware of this, the European Commission recognised the need for member States to continue, at the EU level, the development of guidance on the prevention and control of HAIs.

Common HAIs include infections from invasive procedures, such as Surgical Site Infections (SSIs). Although this type of infections, the second most frequent in Europe, have been shown to be among the most preventable HAIs, the implementation of the measures required to prevent SSIs is not standardised according to the World Health Organisation (WHO).

Catheter-Related Infections (CRIs) are another subcategory of HAIs, which may lead to a critical complication of catheter devices. Like SSIs, CRIs are consistently associated with prolonged hospitalisation, increased mortality and elevated costs. Extended length of stay in hospital is reported to represent the primary cost burden, with additional costs arising from the diagnosis and treatment of infected patients.

Blood Culture Contamination (BCC) is also linked to increased HAIs and a common problem within the hospital setting. BCC (i.e., false positives) often cause patients to be treated with inappropriate and unnecessary antibiotics that can extend hospital length of stay and in turn increase the risk of HAIs or conditions.

Against this background, skin antiseptics represent a critical step in the prevention of infections related to surgical and vascular access procedures and blood culture contamination. This white paper aims at facilitating the prevention of HAIs in the EU and eventually contributing to European's safety by providing a set of evidence-based policy recommendations on skin antiseptics.

It gathers the insights and views of a pan-European group of experts representing European and national stakeholders active in the relevant areas surrounding the topics of SSI, CRI, BCC and skin antiseptics: surgery, hygiene and public health, microbiology, immunology, bacteriology and infectious diseases.

Their recommendations cover two key aspects in skin: which type of antiseptic should be used to maximise prevention and guarantee an optimal level of safety to European patients; and how should it be applied to boost protection and prevent potential adverse events.

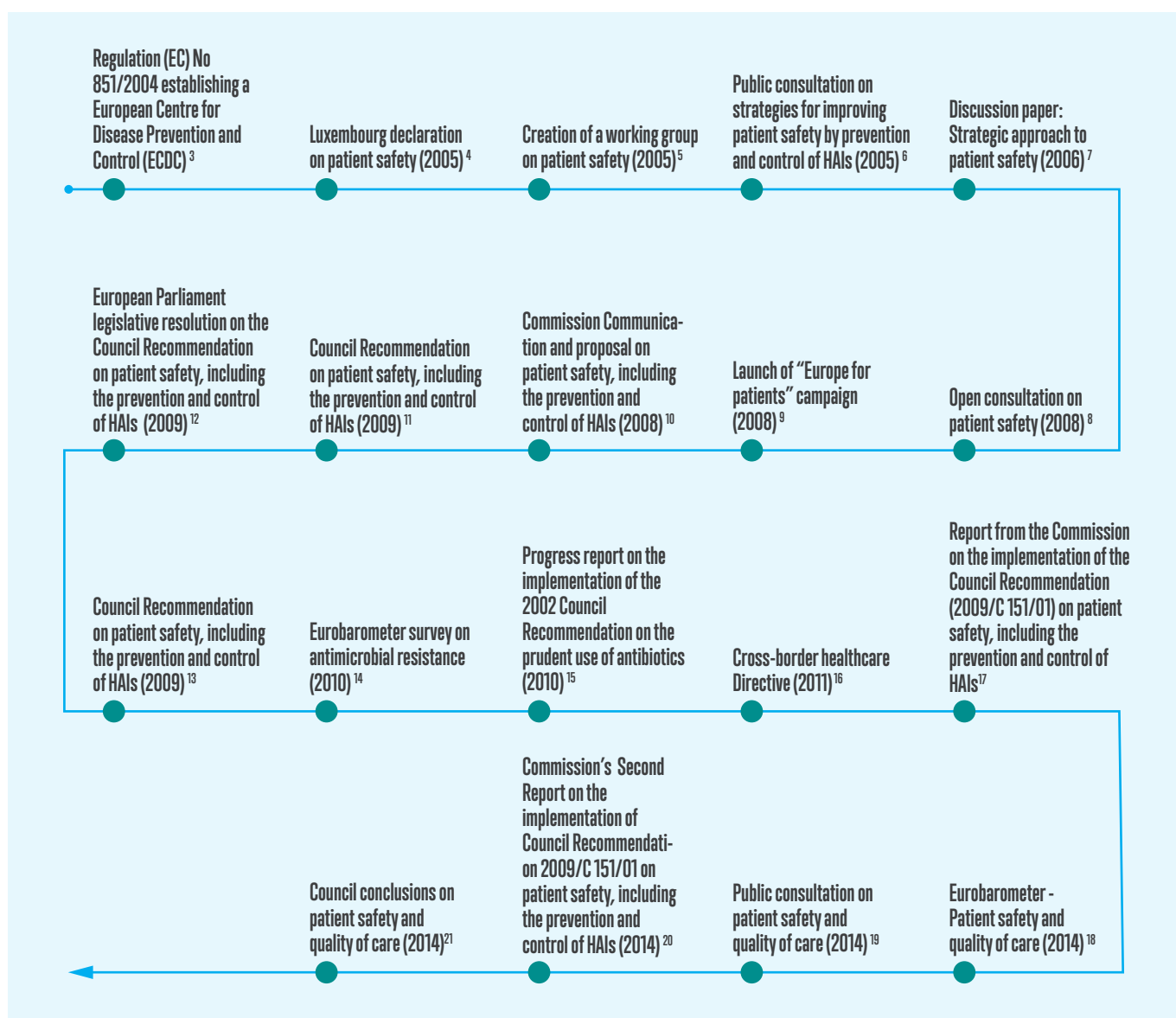
III. PATIENT SAFETY AND HEALTHCARE-ACQUIRED INFECTIONS - RELEVANT CONTEXT IN THE EU

A. POLITICAL BACKGROUND

Under the Lisbon Treaty¹, the Union should strive towards “a high level of human health protection in [...] all Union policies and activities” (Article 168 on public health), by complementing national policies, promoting cooperation and complementarity between health services of Member States, protecting consumers safety and fostering availability and exchange of information and best practices (Article 169 on consumer protection and Article 170 on trans-European networks).

safety in the last decade. These developments -some of which are summarised in the graph below- demonstrate that, as highlighted by the World Health Organisation (WHO)², the definition of patient safety has evolved from untoward events related to health care in hospitals and work around anaesthesia error monitoring to a broader content and context, requiring complex interventions.

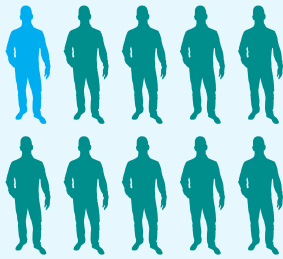
The EU has already taken a number of steps in this direction, which have delivered significant developments in patient



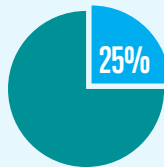
- The Council Recommendation on patient safety (2009)²² called on Member States to enact a series of measures to minimise harm to patients receiving health care and to adopt and implement specific strategies for the prevention and control of HAIs.
- The Council conclusions on patient safety and quality of care (1 December 2014)²³ invited the Commission and Member States to develop voluntary guidelines on how to establish standards and guidelines on patient safety, while taking into consideration existing methodologies as regards setting standards and guidelines used both by national competent authorities and by health professional and scientific associations.

The succession of these relevant legislative and policy milestones related to patient safety lead to one clear conclusion: the EU political action must focus on addressing the specific challenges related to HAIs and in particular on the most common infection types, which include catheter-related infections and surgical site infections.

Healthcare-Associated Infections



HAIs affect (1)
1 in 10 patients



HAIs represent approximately (1)
25% of adverse events

81 089
Europeans on any
given day

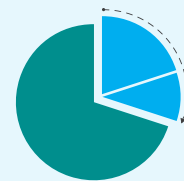
approximately 81 089 Europeans
on any given day (2)



Estimated number of patients
who acquire a HAI in the EU (2)
4.1 million patients every year



HAIs are responsible for (3)
at least 37 000 deaths every year



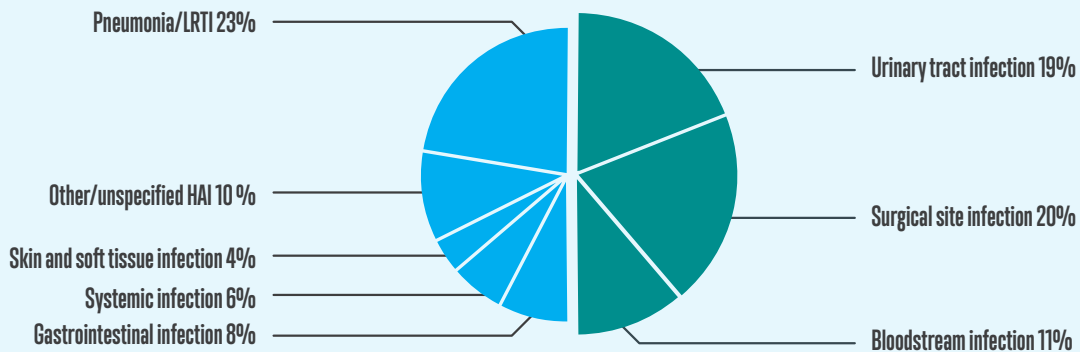
20-30% of HAI
Can be prevented by intensive hygiene
and control programmes (2)

1. Data from the European Commission²⁴

2. Data from the European Centre for Disease Prevention and Control (ECDC)²⁵

3. Data from the ECDC²⁶

Distribution of HAI types in acute care hospitals in EU/EEA, all specialties



Source: European Centre for Disease Prevention and Control (ECDC) ²⁷

Even though all countries have developed specific policies on patient safety or embedded them as priorities in their health policies²⁸, not all countries have implemented specific measures to prevent HAIs and complications during or after surgical intervention²⁹. The Commission recognised the need for member States to continue, at the EU level, the development of guidance on the prevention and control of HAI³⁰ and further stressed that

action in this regard is particularly pressing for HAIs are likely to constitute an increasing proportion of the overall burden of disease in European societies³¹. Factors that explain this burden according to the Commission include the following.³²

Factors behind the increasing burden of HAIs³²

Increased patient mobility

“When patients do seek healthcare in other Member States, it is essential to ensure that the well-being and safety of the patient is properly protected”.

Ageing society

“The increasing numbers of older people will generate a proportionately greater demand for healthcare”.

Rapid spread

“These infections are not constrained by national boundaries and can rapidly spread between countries as evidenced by international spread of MRSA as well as the SARS coronavirus. Taking action in this area seems urgent also in light of the importance of infection control during a possible pandemic.”

Advances in medical treatment

“Health systems across Europe face common challenges as they adapt to constant developments in medical science. Although these health systems are primarily the responsibility of the Member States, cooperation at European level has great potential to bring benefits both to individual patients and to health systems overall”.

“HAI is one of the most prominent reasons for failure of advanced medical treatment such as complicated surgery, intensive care, transplant medicine, and cancer treatment”.

In the specific case of Surgical Site Infections, the European Centre for Disease prevention and Control (ECDC) has produced guidelines on the surveillance of surgical site infections in Europe. However, the EU is still missing recommendations on

how to address and prevent the many factors that have been identified as contributing to the risk of surgical site infections and the role of skin antiseptics in this regard.



RECOMMENDATION 1

Open a new phase in the prevention of healthcare associated infections by making the fight against the most common healthcare associated infections, and in particular against surgical site infections and catheter-related infections, a priority in the political agenda on patient safety.

B. SURGICAL SITE INFECTIONS AND CATHETER-RELATED BLOODSTREAM INFECTIONS, A CLINICAL THREAT

Surgical Site Infections (SSIs) are gaining positions in the ranking of the most frequent types of HAI in Europe: they went from the third most common in 2012³³ to the second most common in 2016³⁴. Given that the number of surgical procedures is increasing in the EU³⁵, situation is not likely to improve unless specific measures are taken.

However, as recognised by the WHO, the implementation of the measures required to prevent SSI is not standardised international guidelines are currently available.

“While some national guidelines are available, especially in Europe (...), several inconsistencies have been identified in the interpretation of evidence and recommendations and validated systems to rank the evidence have seldom been used. Importantly, none

*of the currently available guidelines have been based on systematic reviews conducted ad hoc to provide evidence-based support for the development of recommendations”.*³⁶

World Health Organisation (WHO)

In addition, the WHO further highlighted that globally relevant topics which, if neglected, can lead to potentially harmful consequences for the patient are mentioned only in few sectorial guidelines.³⁷

SSIs are associated with longer postoperative hospital stay, additional surgical procedures or stay in an intensive care unit and often higher mortality.³⁸ Prolonged hospitalisation and increased morbidity due to a SSI negatively impact patient health-related quality of life³⁹.

In European hospitals, patients who develop an SSI constitute a financial burden approximately



double that of a patient without an infection

The length of hospitalisation is



over twice as long for patients with an SSI

Broex EC, van Asselt AD, Bruggeman CA, van Tiel FH. 2009. “Surgical site infections: how high are the costs?”⁴⁰

SSIs, CRIs and Antimicrobial Resistance (AMR)

Most surgical site infections can be treated with antibiotics.⁴¹

The antibiotic given to patient depends on the bacteria causing the infection. Sometimes patients with SSIs also

need another surgery to treat the infection, and hence an increased use of antibiotics.⁴²

In other words, reducing SSIs and CRIs contributes to reducing the overall use of antibiotics, which is a cornerstone action in the fight against AMR.

HAIs can also be associated with the devices used in medical procedures, such as catheters (e.g., catheter-associated urinary tract infections) or ventilators (ventilator-associated pneumonia).⁴³ A device-associated HAI is defined as a HAI in a patient with a (relevant) device that was used within the 48-hour period before onset of infection (even if it was used only intermittently).⁴⁴ The term ‘device-associated’ is only used for pneumonia, bloodstream infections, and urinary tract infections.⁴⁵

Within this group, **Catheter-Related Infections CRIs** are particularly prevalent. There is a general agreement that, together with SSIs, CSRBI also represent a significant burden in terms of impact on patient outcomes and overall costs.⁴⁶

CRIs are also consistently associated with prolonged hospitalisation, increased mortality and elevated costs. Extended length of stay in hospital is reported to represent the primary cost burden, with additional costs arising from the diagnosis and treatment of infected patients.^{47 48 49 50} Furthermore, CRIs often affect people with comorbidities (such as cancer or patients undergoing a dialysis treatment), which may worsen their clinical outcomes.

While their substantial clinical burden to patients is clearly proven, the impact on patient quality of life and psychological wellbeing is seldom considered when assessing their true full cost.

C. CONTAMINATION OF BLOOD CULTURES, A PRE-CLINICAL CHALLENGE AND CONTRIBUTING FACTOR TO AMR

While **Blood Cultures** play an important role in the diagnosis of serious infections, Blood Cultures Contamination (BCC) (i.e. false-positive blood cultures) is also a common problem within the hospital setting. BCC result in unnecessary repeated testing and they often cause patients to be treated with inappropriate and unnecessary antibiotics that can extend hospital length of stay, which in turn increase costs and the risk of HAIs.^{53 54 55}

The American Society for Microbiology and the Clinical and Laboratory Standards Institute recommended that an acceptable rate of blood culture contamination should not exceed 3%.⁵⁶

BCC, a contributing factor to Antimicrobial resistance (AMR)

Almost half of the patients with BCC and hence a false-positive result are **unnecessarily** treated with antibiotics.⁵¹ As a result, patients are placed at risk for serious adverse events with no clinical benefit.

The misuse of antibiotics contributes to increasing the challenge posed by antibiotic resistance, already one of the most serious and growing threats to public health.⁵²



RECOMMENDATION 2

Promote EU-level guidelines or recommendations on skin antiseptics which specifically address the prevention of surgical site infections, catheter-related bloodstream infections and blood culture contamination as the leading contributing factors to healthcare-associated infections.



RECOMMENDATION 3

Promote skin antiseptics in the framework of any relevant ongoing and upcoming political initiative on Antimicrobial Resistance and in particular in the European Commission ‘Action Plan Against the rising threats from Antimicrobial Resistance: Road Map’, so as to reduce the unnecessary use of antibiotics due to blood culture contamination and decrease the consumption of antibiotics by reducing Surgical Site Infections (SSI) and Catheter-Related Infections (CRIs).

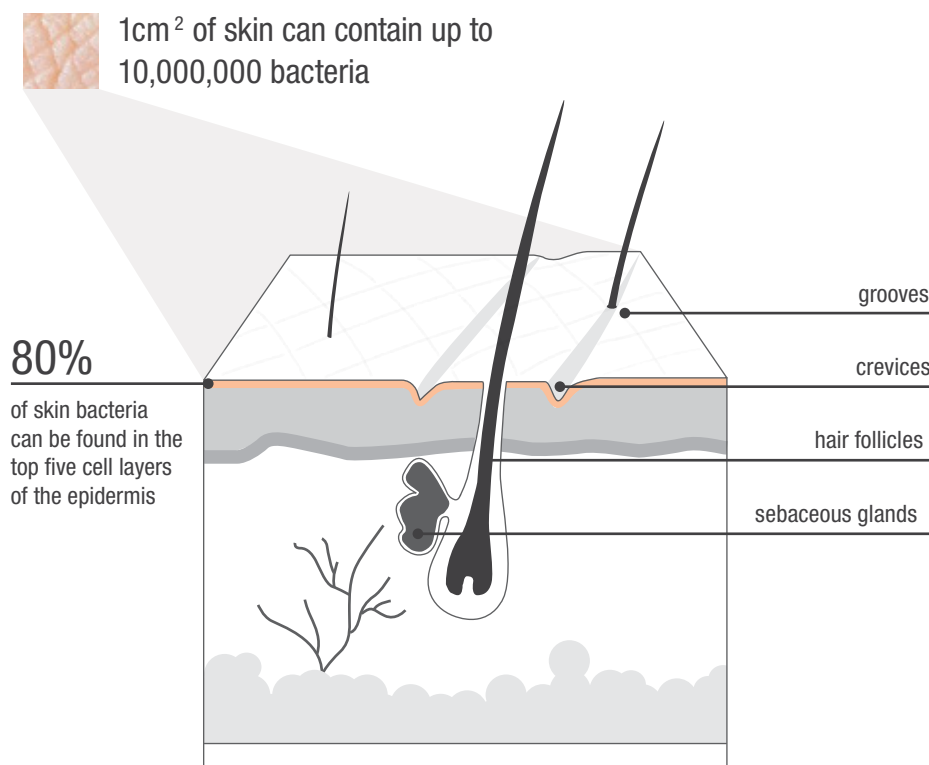
IV. WHY IS SKIN ANTISEPSIS CRITICAL

The human skin harbours up to 10^6 bacteria per cm^2 , most of which (80%) are found within the first five superficial cell layers of the epidermis.^{57 58 59 60}

Indeed, patient endogenous skin flora is believed to be the source of infection in the majority of post-operative infections⁶¹ as well as catheter-related infection.^{62 63 64}

Whether it be for a surgical incision or a puncture for injections, the procedure disrupts the skin integrity and its function as barrier against infection. This means that, if microbes are not successfully removed from the skin prior to puncture or incision, they may access the bloodstream or body tissue.

Hence, skin antisepsis represents a critical step in the prevention of infections related to surgical and vascular access procedures and blood culture contamination, i.e., false positive blood culture.



V. MEDICINAL PRODUCTS OR BIOCIDES? A REGULATORY ISSUE

Depending on the intended application, antiseptic products may fall under different legal frameworks (they are ‘borderline products’), including the biocidal products legislation⁶⁵ and medicinal products legislation.⁶⁶ Within the European Union, the classification of disinfectants is not uniform.

The Commission recognised that the determination of a clear borderline between the Biocidal Products Directive 98/8/EC⁶⁷ (nowadays replaced by the Biocidal Product Regulation (BPR, Regulation (EU) 528/2012⁶⁸) and the Human Medicinal Products Directive 2001/83/EC, as amended by Directive 2004/27/EC, is a crucial issue for the proper implementation of both pieces of legislation.⁶⁹ The Commission also added that there are many borderline cases which have been identified so far and that practical guidance and examples are needed.⁷⁰

According to a European Chemicals Agency (ECHA) draft guidance document on the Biocidal Products Regulation “*products for disinfection of (...) undamaged skin before a medical treatment of a patient (e.g. pre-operative skin*



antiseptics before surgery and disinfection before skin puncture) (...), are always medicinal products”.⁷¹




Due to this lack of clarity at an EU level, the legal definitions for biocidal and medicinal products are not interpreted uniformly by the Member States. Several EU Member States’ health authorities regard all preoperative skin disinfectants as medicinal products while some other countries (Italy, Spain) regard all products used on intact skin as biocidal products, including antiseptics used on patients.

While this may be perceived as a pure classification issue that only affects the individual assessment of the specific products, it raises a more general concern: some Member States allow and accept the use of biocidal products as medicinal products although those products do not have a marketing authorisation under the legislation regulating medicinal products. This also means that they are subject to different controls and standards which can potentially lead to inadequate decontamination of the preoperative intact skin area as well as patient harm.

KEY DIFFERENCES

There are key differences between a biocidal product and a medicinal product in several aspects such as:

| MEDICINES | | BIOCIDES |
|--|---|---|
| <ul style="list-style-type: none"> EMA’s scientific guidelines on the clinical efficacy and safety of human medicines help applicants prepare marketing authorisation applications. Clinical trials are carried out in a regulated way in healthy people and patients. Efficacy, safety and quality of every single product tested by a competent licensing body. Evidence must be furnished during the marketing authorisation procedure, in view of the benefits and potential risks of the product. | <p>Demonstration of quality, safety and efficacy</p>  | <ul style="list-style-type: none"> Experiment or tests for the purposes of research or development involving an unauthorised biocidal product or a non-approved active substance intended exclusively for use in a biocidal product are carried out under the conditions laid down in BPR. |
| <ul style="list-style-type: none"> Legislation requires medicinal products for human use manufactured or imported into EU, to be in accordance with the guidelines of good manufacturing practice (GMP). | <p>Manufacturing and sterility</p>  | <ul style="list-style-type: none"> No specific requirements for the manufacturing process. No sterility or microbiological controls required. |

| MEDICINES | | BIOCIDES |
|--|---|---|
| <ul style="list-style-type: none"> • Strict legislative requirements on quality management system and pharmaceutical quality assurance system etc. • Manufacture of medicinal products subject to constant official supervision and to a pharmacovigilance system. • Manufacture of sterile products subject to special requirements minimising risks of microbiological contamination. | <p>Manufacturing and sterility</p>  | |
| <ul style="list-style-type: none"> • Suppliers subject to control and audit under the GMPs to verify compliance with the specifications of the raw material supplied and compliance with the GMP. • Suppliers are defined in the registry and subject to approval and control of changes and must indicate to the competent Authority and customers who purchase the product any change. | <p>Supply chain</p>  | <ul style="list-style-type: none"> • No control of suppliers of the raw material required. • For co-formulants there is no specific indication and any co-formulant can be used but for the active substance, it is required to buy it from suppliers listed in art. 95 of the BPR. |
| <ul style="list-style-type: none"> • Community Register lists all medicinal products for human and veterinary use as well as orphan medicinal products that have received a marketing authorisation through the centralised procedure. • Some Member States established registers of nationally-authorized medicinal products. | <p>Registry</p>  | <ul style="list-style-type: none"> • Union Register for Biocidal Products. |

In skin antiseptics, the sterility of the solution is an important aspect to be considered.

In the EU, the Medicinal Products Directive in conjunction with the existing provisions on sterilisation (annexes to pharmaceutical development decision trees on the sterilisation of human and veterinary medicinal products that will be replaced with the EMA Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container, when adopted⁷²) guarantee the sterility of all medicinal products.

IMPLICATIONS

The use of biocides for a medicinal purpose does not only contradict the purpose of the biocidal products' and medicinal products' provisions, but it also raises concerns from the patient and occupational safety standpoints as well as from the environmental and antimicrobial resistance perspectives.

However, in non-sterilised antiseptic solutions, contamination by certain bacteria or spores may occur during the manufacturing process (intrinsic contamination), as broadly documented in the literature.^{73 74 75 76 77}

In 2007, only in the US, more than 40 outbreaks and pseudo-outbreaks due to contaminated antiseptics were reported.⁷⁸ In Spain, batches of antiseptic solutions (classified as biocides) had to be recalled from the market due to contamination.⁷⁹



PATIENT SAFETY

We have established that Biocides and medicines are subject to very different regulatory routes which confer different standards in term of safety efficacy and quality. It therefore follows that using biocidal products as medicines, while biocides do not have a marketing authorisation under the legislation regulating medicinal products may jeopardise patient's safety.

As highlighted by the MHRA, there are health risks associated with that practice and "Using the appropriately authorised product for its specific intended use, in accordance with the manufacturer's instructions for use, is the best way of minimising harm".⁸⁰ Studies have shown that biocides can have toxic, carcinogen and endocrine disrupting properties⁸¹.



ANTIMICROBIAL RESISTANCE

The former European Commission Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) stressed⁸² that, in order to preserve the role of biocides in infection control and hygiene, it is paramount to prevent the emergence of bacterial resistance and cross-resistance through their appropriate and prudent use. "*The need for proper use of disinfectant and antiseptics should be stressed and health care workers should be trained to comply with clear and agreed policies and practices, avoiding unnecessary and incorrect use of biocides*", they added.⁸³

In other words: in the specific case of skin antiseptic prior to medical treatments, the use of biocides must be limited to those cases where it is strictly required and no other similar or more suitable alternative to the biocide, such as a medicine, could be used instead.

Furthermore, as explained in the introductory section of this paper, the misuse of antibiotics following false positive blood cultures does not only place patients at risk for serious adverse events with no clinical benefit, but contributes to an increased antimicrobial resistance.



OCCUPATIONAL SAFETY

Healthcare workers can be exposed to biocides either directly (primary exposure, i.e., the worker/operator actively uses the biocidal product) or indirectly (secondary exposure, i.e., after the actual use or application of biocidal products). As mentioned above, biocides may have toxic, carcinogen and endocrine disrupting properties, which, especially in the case of workers, may be undetectable.

Under the Carcinogens and Mutagens Directive 2004/37/EC the employer must ensure that the risk to workers' health and safety from dangerous substances is eliminated or reduced to a minimum (first level in the hierarchy of risk control). In order to fulfil this obligation, the first priority for the employer is to substitute or eliminate the risk of biocides, which can be done by using alternative disinfectants or replacing them with less harmful procedures, substances, preparations or products.

While various European and national guidelines exist providing instructions for working safely with disinfections in the healthcare sector, the EU is lacking harmonised specific guidelines on the safe use of biocides in the healthcare sector. The European Commission DG Employment guideline provided a general description of good practice on safe working in disinfection activities⁸⁴ which didn't dwell on biocides and the use of these in the healthcare sector.



ENVIRONMENTAL IMPACT

The use of biocides can also have significant adverse effects the natural environment. In the healthcare sector, disposal of used or unwanted biocides must be undertaken carefully to avoid serious and potentially long-lasting damage to the environment.



RECOMMENDATION 4

Promote EU guidelines/recommendations to clarify and promote a harmonised approach across the EU on the classification of skin disinfectants before surgery and insertion.

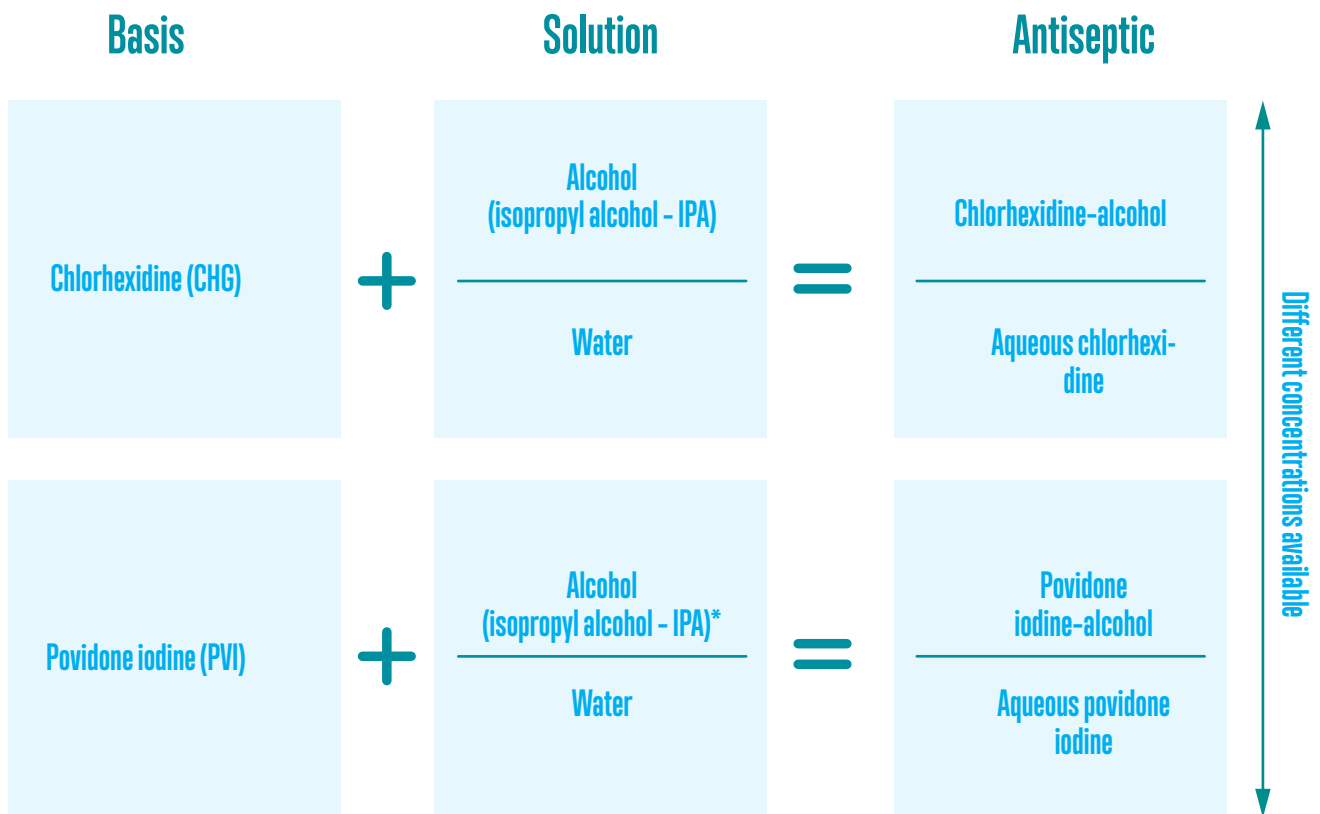
VI. OPTIMISING SKIN ANTISEPSIS TO PREVENT INFECTIONS

We have established that, since the patient’s skin is a major source of pathogens, preoperative treatment of the intact skin is key to reduce the microbial load on the patient’s skin as much as possible before incising the skin barrier.

Despite skin antiseptics preventive measures before medical interventions are now well established, SSIs, CRIs and BCCs are still commonplace and remain a significant challenge. This calls for policy measures that preserve European patients’ safety by

optimising preoperative skin antiseptics.

The most widely-used antiseptics are chlorhexidine gluconate (CHG) and iodophors (such as povidone iodine [PVI]) in alcohol-based solutions, which are effective against a wide range of bacteria, fungi and viruses. Aqueous solutions, particularly those containing iodophors, are also widely used, notably in developing countries.⁸⁵



Overall, chlorhexidine-alcohol (in particular 2% Chlorhexidine in 70% Isopropyl Alcohol) in single use sterile applicator has proven to reduce the incidence of infections by 61.9%.⁸⁶

It has also proven superior to other preparations for disinfection. 2% Chlorhexidine in 70% Isopropyl Alcohol (from now onwards always referred to as “chlorhexidine-alcohol”**) in a single use sterile applicator has demonstrated to be more effective than aqueous povidone iodine in preventing SSIs after clean (incision in which no inflammation is encountered in a surgical procedure, without a break in the respiratory, alimentary and genitourinary tracts) and contaminated surgery (reducing the

overall incidence of SSIs by 41%)⁸⁷ and to alcoholic povidone iodine in cardio-thoracic surgery (reducing the incidence of SSI by 63%)⁸⁸ and in C-section surgery (reducing the incidence of SSI by 45%).⁸⁹ Furthermore, it offers demonstrable increased protection to post-operative skin incision sites from infections derived from bacteria inhabiting the lower layers of skin.⁹⁰

Evidence also shows that chlorhexidine-alcohol in single use sterile applicator significantly and durably decreases the rates of CRIs⁹¹ to a greater extent than alcoholic povidone⁹² (up to 84%)⁹³.

Chlorhexidine-alcohol in single use sterile applicator has

* Some countries (e.g., France) use ethanol instead, which is less effective than IPA.

** Although different concentrations exist, for reasons of simplification, any mention to “chlorhexidine-alcohol” refers to the solution ‘2% Chlorhexidine in 70% Isopropyl Alcohol’.

repeatedly demonstrated successful in reducing reduce the rate of blood culture contamination, when compared to various alternative skin disinfectants used before blood collection.^{94 95}

^{96 97 98 99} Evidence of the efficacy and efficiency of chlorhexidine-

alcohol (single use sterile applicator) in skin antiseptics prior to blood collection for transfusion has led to its adoption by leading Blood collection organisations worldwide (UK-NHS-Blood Services, American Red Cross, Canadian Red Cross).






RECOMMENDATION 5

Promote EU guidelines on skin antiseptics as a relevant factor for patient safety and the prevention of HAI's, recommending the use of sterile 2% Chlorhexidine in 70% Isopropyl Alcohol (in the absence of specific contraindications) as the safest and most efficient solution for the prevention of healthcare-associated infections.

RECOMMENDATIONS AND GUIDELINES

The body of evidence in favour of chlorhexidine-alcohol has resulted in this solution being integrated and recommended in guidelines in several countries. The following is a non-exhaustive list of those organisations or institutions which have recommended the use of this solution for an optimal disinfection of the skin.

| ORGANISATION/ INSTITUTION YEAR | TITLE |
|--|---|
| World Health Organisation (WHO) 2010  | WHO Guidelines on drawing blood: best practices in phlebotomy* ¹⁰⁰ <i>"Health workers should clean the skin with a combination of 2% chlorhexidine gluconate in 70% isopropyl alcohol, covering the whole area and ensuring that the skin area is in contact with the disinfectant for at least 30 seconds".</i> |
| World Health Organisation (WHO) 2016  | WHO Global Guidelines for the prevention of Surgical Site Infection ^{101 102} <i>"The panel recommends alcohol-based antiseptic solutions based on CHG for surgical site skin preparation in patients undergoing surgical procedures." (Strong recommendation**)</i> |
| National Institute for Health and Care Excellence (NICE), UK 2014  | Quality statement 61 – infection prevention and control ¹⁰³ <i>"The skin should be decontaminated at the insertion site with 2% chlorhexidine gluconate in 70% alcohol and allowed to dry before inserting a vascular access device."</i> |

* Phlebotomy is the process of making an incision in a vein with a needle.

** The members of the WHO Guidelines Development Group qualified the direction and strength of each recommendation by considering the quality of evidence and other factors, including the balance between benefits and harms, the values and preferences of stakeholders and the resource implications of the intervention. Levels of recommendations' strength were classified as strong or conditional. Quality of evidence was classified as moderate, low or very low.

| | |
|---|--|
| <p>Department of Health, UK 2014</p>  <p>Department of Health</p> | <p>Epic3: National Evidence-Based Guidelines for Preventing Healthcare-Associated Infections in NHS Hospitals in England ¹⁰⁴</p> <p>CUTANEOUS ANTISEPSIS</p> <p><i>“IVAD14 Decontaminate the skin at the insertion site with a single-use application of 2% chlorhexidine gluconate in 70% isopropyl alcohol (or povidone iodine in alcohol for patients with sensitivity to chlorhexidine) and allow to dry prior to the insertion of a central venous access device.” (Class A^{***})</i></p> <p><i>“IVAD15 Decontaminate the skin at the insertion site with a single-use application of 2% chlorhexidine gluconate in 70% isopropyl alcohol (or povidone iodine in alcohol for patients with sensitivity to chlorhexidine) and allow to dry before inserting a peripheral vascular access device.” (New recommendation Class D/GPP^{****})</i></p> <p>CATHETER AND CATHETER SITE CARE</p> <p><i>“Use a single-use application of 2% chlorhexidine gluconate in 70% isopropyl alcohol (or povidone iodine in alcohol for patients with sensitivity to chlorhexidine) to clean the central catheter insertion site during dressing changes, and allow to air dry.” (Class A)</i></p> <p><i>“Use a single-use application of 2% chlorhexidine gluconate in 70% isopropyl alcohol (or povidone iodine in alcohol for patients with sensitivity to chlorhexidine) to clean the peripheral venous catheter insertion site during dressing changes, and allow to air dry.” (New recommendation Class D/GPP)</i></p> <p>GENERAL PRINCIPLES FOR CATHETER MANAGEMENT</p> <p><i>“IVAD30 A single-use application of 2% chlorhexidine gluconate in 70% isopropyl alcohol (or povidone iodine in alcohol for patients with sensitivity to chlorhexidine) should be used to decontaminate the access port or catheter hub. The hub should be cleaned for a minimum of 15 s and allowed to dry before accessing the system.” (Class D/GPP)</i></p> |
| <p>Department of Health, Ireland 2011</p>  <p>DEPARTMENT OF HEALTH</p> | <p>Community Infection Prevention and Control Manual ¹⁰⁵</p> <p>CLEANING THE CATHETER SITE</p> <p><i>“In adults and children (>2months) a single patient use application of alcoholic chlorhexidine gluconate solution (preferably 2% chlorhexidine gluconate in 70% isopropyl alcohol) should be used to clean the CVC^{*****} site prior to insertion and during dressing changes and allowed to air dry”.</i></p> <p>CVC USE AND MAINTENANCE</p> <p><i>“The injection port or catheter hub should be disinfected with 2% chlorhexidine gluconate in 70% isopropyl alcohol and allowed to dry before it is used to access the system (unless contraindicated by the manufacturer).”</i></p> <p>PERIPHERAL INTRAVASCULAR CATHETER (PVC) INSERTION</p> <p><i>“In adults and children >2 months a single patient use application of 2% chlorhexidine gluconate in 70% alcohol should be used to disinfect the skin prior to insertion. Skin which is visibly soiled should be first cleaned with soap and water prior to disinfection.”</i></p> <p>CARE OF THE INSERTION SITE AND HUB</p> <p><i>“The hub/injection port should be disinfected with 2% chlorhexidine gluconate in 70% alcohol (preferred) and allowed to dry prior to accessing the cannula to administer medications or fluids.”</i></p> |

*** This guidance is based on the available evidence. The type and class of supporting evidence explicitly linked to each recommendation is described. Recommendations were graded A to D or noted as a Good Practice Point (GPP) recommendation.

**** A good practice point (GPP) is a recommendation for best practice.

***** Central Venous Access Devices (CVCs).

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| <p>Health Protection Scotland 2012</p>  | <p>What are the key infection prevention and control recommendations to inform a surgical site infection (SSI) prevention quality improvement tool? ¹⁰⁶</p> <p><i>“Final recommendation – Ensure that 2% chlorhexidine gluconate in 70% isopropyl alcohol solution is used for skin preparation (if patient sensitive, use povidone-iodine.” (Category 1B*)</i></p> |
| <p>French Society for Hospital Hygiene (SF2H) 2016</p>  | <p>Antiseptie de la peau saine avant un geste invasif chez l’adulte Recommandations pour la pratique clinique ¹⁰⁷</p> <p><i>“Before insertion of an intravascular catheter it is strongly recommended to use an alcoholic solution of 2% chlorhexidine rather than an alcoholic solution of povidone iodine in intensive care (A-1**) as well as in all other sectors (A -3).”</i></p> |
| <p>Infusion Nurses Society 2016</p>  | <p>Infusion Therapy standards of practice ¹⁰⁸</p> <p>IMPLANTED VASCULAR ACCESS PORTS</p> <p><i>“Use the preferred skin antiseptic agent of >0.5% chlorhexidine in alcohol solution.” (I) ***</i></p> <p>SHORT PERIPHERAL AND MIDLINE CATHETERS</p> <p><i>“Perform skin antiseptis using the preferred skin antiseptic agent of >5% chlorhexidine in alcohol solution”. (I)</i></p> <p>ARTERIAL CATHETERS</p> <p><i>“Perform skin antiseptis using the preferred skin antiseptic agent of >0.5% chlorhexidine in alcohol solution”. (I)</i></p> <p>VASCULAR ACCESS DEVICE (VAD) ASSESSMENT, CARE AND DRESSING CHANGES</p> <p><i>“Perform skin antiseptis as part of the site care procedure: 1. The preferred skin antiseptic agent is >0.5% chlorhexidine in alcohol solution”. (I)</i></p> |
| <p>US Centers for Disease Control and Prevention (CDC) 2011</p>  | <p>Guidelines for the Prevention of Intravascular Catheter-Related Infections ¹⁰⁹</p> <p>SKIN PREPARATION RECOMMENDATIONS</p> <p><i>“1. Prepare clean skin with an antiseptic (70% alcohol, tincture of iodine, an iodophor or chlorhexidine gluconate) before peripheral venous catheter insertion [82].” Category IB ****</i></p> <p><i>“2. Prepare clean skin with a >0.5% chlorhexidine preparation with alcohol before central venous catheter and peripheral arterial catheter insertion and during dressing changes. If there is a contraindication to chlorhexidine, tincture of iodine, an iodophor, or 70% alcohol can be used as alternatives.” Category IA</i></p> |

* Grade of recommendation based on review of evidence.

** The strength of each recommendation (from A to E) and its level of proof (from 1 to 3) according to the criteria of the French High Authority of Health.

*** The rating scale for the strength of the body of evidence ranges from the highest rating of “I,” representing a meta-analysis and other research on research to the lowest level of “V.”

**** Each recommendation is categorised on the basis of existing scientific data, theoretical rationale, applicability, and economic impact. The system for categorising recommendations in this guideline is as follows:

- Category IA. Strongly recommended for implementation and strongly supported by well-designed experimental, clinical, or epidemiologic studies.
- Category IB. Strongly recommended for implementation and supported by some experimental, clinical, or epidemiologic studies and a strong theoretical rationale; or an accepted practice (e.g., aseptic technique) supported by limited evidence.
- Category IC. Required by state or federal regulations, rules, or standards.
- Category II. Suggested for implementation and supported by suggestive clinical or epidemiologic studies or a theoretical rationale.
- Unresolved issue. Represents an unresolved issue for which evidence is insufficient or no consensus regarding efficacy exists.

COST-EFFICIENCY

Numerous studies have assessed the cost and economic impact of chlorhexidine-alcohol in single use sterile applicator, proving that the switch from other solutions to chlorhexidine-alcohol leads to significant cost savings.¹¹⁰

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**VII. PREVENTING ADVERSE
EVENTS IN SKIN
ANTISEPSIS: "IT'S NOT
ONLY WHAT YOU USE, IT'S
THE WAY YOU USE IT"**

Once established what is the optimal skin antiseptics prior to surgical incision or insertion of intravascular catheters, another key element needs to be addressed: the method of application of the antiseptic agent.

and reduce waste. A single-use applicator may also potentially encourage a standardised and more thorough approach to skin preparation, offering reduction of the risk of cross-contamination during antiseptic application.¹¹³

From a patient safety standpoint, the way the skin antiseptic is applied may be equally important as the selection of the product for it affects safety, standardisation and practicality and facilitates the change to an evidence-based technique. For example, a single-use applicator has the potential to control the antiseptic volume, reduce medication errors, save time

However, most guidelines in the EU focus on antiseptic agents with little consideration of the importance of application methods.¹¹⁴ The exceptions are those from Spain¹¹⁵, which specifically suggest that an applicator is preferred, and a ‘back and forth’ application method for 30 seconds is recommended¹¹⁶.



RECOMMENDATION 6

Consider the method of application of the skin antiseptic in the guidelines on skin antiseptics, with a special focus on single-use applicators.

While relatively few recent studies have assessed the effectiveness of applicators for skin antiseptics, empirical benefits and

published studies consistently suggest that single-use applicators offer advantages over multiple-use bottles and gauze.^{117 118}

OVERVIEW OF BENEFITS ASSOCIATED WITH SPECIFIC FEATURES OF THE 2% CHLORHEXIDINE IN 70% IPA IN SINGLE USE STERILE APPLICATOR:

| Feature | Benefit |
|--|---|
| Sterile solution | <ul style="list-style-type: none"> Terminal sterilisation of the solution prevents contamination by certain bacteria or spores that may occur during the manufacturing process (intrinsic contamination) as documented for non-sterilised solution. |
| Sterile single use applicator | <ul style="list-style-type: none"> Single use prevents cross-contamination and / or extrinsic contamination of multi-use bulk bottle. Survival of bacteria species and spores has been demonstrated in antiseptic solutions. |
| “Enclosed system” | <ul style="list-style-type: none"> The sterile antiseptic solution is contained in a hermetic ampoule and is released only at the time of use. This avoids manipulation and pouring, preventing any confusion and/or accidental injection of the antiseptic. It also reduces the risk of possible spilling or splashing of the intervention field. |
| Sterile applicator | <ul style="list-style-type: none"> Enables aseptic non-touch technique. |
| Sponge allows easy control of the solution’s flow | <ul style="list-style-type: none"> The right volume is applied. This prevents pooling of solution, minimising risk of chemical or thermal burns (including operation room fire) and inhalation of alcoholic vapours. It reduces time for the solution to dry. It also minimises waste of solution and contamination of the environment. |

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| <p>Back and forth movement</p> | <ul style="list-style-type: none"> • The applicator facilitates gentle friction with the back and forth movement. • Back and forth application allows penetration of the antiseptic solution in top cell layers of the epidermis, where 80% of bacteria reside, improving anti-bacterial efficacy. It also eliminates superficial dead cells containing a high amount of pathogens. • 30" application with back and forth movement on the incision site – then moving to the periphery – is simple to implement and standardise, facilitating compliance to best practice. • Reducing variability of preparation technique improves quality of care. |
| <p>Single-step skin antiseptics ("all in one")</p> | <ul style="list-style-type: none"> • Reducing the number of steps to prepare the skin facilitates a simple and standardised procedure. • Clinical studies demonstrate the efficacy of a one-step disinfection process on clean skin. • The system reduces ancillary materials (gallipot, gauze, forceps) and reduces overall waste. |

A. STERILE SOLUTION

Contamination of antiseptic solutions has been broadly reported in the literature.^{119 120 121 122 123 124 125}

In 2007, only in the US, more than 40 outbreaks and pseudo-outbreaks due to contaminated antiseptics were reported.¹²⁶

In Spain, batches of aqueous chlorhexidine had to be recalled from the market due to contamination.¹²⁷

The US FDA, “in order to provide users with important information about contamination that may occur during the manufacturing process”, asked the (...) manufacturers to voluntarily revise the product labels for topical antiseptics to indicate whether the drug is manufactured as a sterile or nonsterile product. “We believe this will assist health care professionals in making informed decisions about using these products.” In the EU, some European health authorities (such as MHRA) now require that for any new pharmaceutical licence, pre-operative skin solution is sterilised.

B. SINGLE USE

Studies have shown that various bacteria may survive up to 14 days in antiseptic solutions.¹²⁸

In view of this, guidelines increasingly recommend the “single use” of skin antiseptics¹²⁹ to prevent cross-contamination (between patients), as well as the risk of contamination of “multi-dose” bottles.

US FDA requires that antiseptics for preoperative skin preparation is provided in single use containers¹³⁰ “to further reduce the risk of infection with improper topical antiseptic use and the possibility of these products becoming contaminated with bacteria during use”. To guarantee this, it specifies that the antiseptics in these single-use containers should be applied only one time to one patient and that applicators and any unused solution should be discarded after the single application.

C. ENCLOSED SYSTEM

Cases of accidental injection of antiseptics have been recorded and reported, with potentially very severe consequences to patients.^{131 132 133}

This can be prevented using enclosed systems, where the antiseptic solution is contained and protected in a hermetic ampoule and only released immediately prior to application, on

the sponge, to be applied directly on the skin.

The system limits the risk of contaminating instruments with the solution, especially when the intervention involves neural tissues.¹³⁴ It also prevents that solution is left to stand in gallipot, with possible evaporation, if the procedure is delayed for any reason.

D. CONTROLLING THE FLOW AND APPLYING THE RIGHT VOLUME OF SOLUTION

This delivers benefits such as:

Preventing burns and fires

The applicator prevents splashing and pooling - minimising the risk of thermal burns and operating room fire, recognised risks when using alcoholic solutions. Surgical fires, though rare, can have devastating consequences for patients, staff, and the healthcare facility.^{135 136 137 138 139 140}

The FDA has published strict recommendations for the prevention of operating room fires (Preventing Surgical Fires Initiative¹⁴¹) that include the use of alcoholic skin antiseptics¹⁴².

The Royal College of Surgeon (RCS) in the UK also published recommendations in this regard¹⁴³, echoing a quote from the Center for Medicaid which stated that, *“to reduce the incidence of pooling and an excess application of alcohol based-skin preparation fluid”, “alcohol-based preparation solutions should be applied using a purpose-built applicator”*.

Reducing drying time and overall time for pre-operative skin washing

Aqueous solutions typically require several minutes (5'-6') to dry. Removing the solution with drapes to speed up the procedure may compromise the antiseptic efficacy.

Alcoholic solutions dry quickly due to evaporation. However, the excessive volume applied with bulk solutions results in variable drying times. Applying the appropriate volume in a standardised method and allowing appropriate dry time reduces the variables and therefore improves compliance, eases the application procedure and leads to better performance¹⁴⁴.

Reducing amount of left-over solution

This is important not only from a cost-efficiency perspective but also to prevent contamination of the environment.

E. ENABLING GENTLE FRICTION WITH BACK & FORTH MOVEMENT

An important prerequisite of effective disinfection is to ensure that the area has adequate amounts of disinfectant applied.

Traditionally, skin antiseptics have been applied in concentric circles working out from the intended procedural site, although there is no evidence to support this procedure. The concentric circle method is required when using aqueous-based products,

which need additional drying time to prevent reintroduction of contaminants to previously cleansed areas.¹⁴⁵

Around 20% of bacteria live in the deeper layers of the skin, among dead skin cells, sweat glands and hair follicles, making it difficult to adequately decontaminate the skin. Back-and-forth friction has been suggested to cleanse more skin layers

and this reduces the bacterial load of the epidermal layer more effectively.¹⁴⁶

Gentle friction with back and forth movement, during thirty

seconds at the insertion or incision site, then moving to the periphery, allows the solution to better reach and kill the bacteria present in the epidermis. This method has shown to be more efficacious than the traditional spiral movement.^{147 148}

F. SINGLE-STEP SKIN ANTISEPSIS

Chlorhexidine-alcohol in single use sterile applicator is an all-in-one system for skin antiseptics.

On clean skin, chlorhexidine-alcohol in single use sterile applicator allows a “single-step” disinfection process, with only one application of the antiseptic solution^{149 150} in contrast to some traditional procedures still requiring a preliminary scrub or two applications of the antiseptic¹⁵¹:

1. Skin washing

Because the skin must be free of soil, debris, exudates and transient microorganisms to minimise contamination before application of the antiseptic skin preparation, washing the specific part of the skin is recommended when it is grossly contaminated by different debris.¹⁵²

2. Skin antiseptics

Application of the actual antiseptic solution at the insertion or incision site, immediately before the procedure.

This provides several benefits including:

Improving compliance to a standardised procedure

A major component to improve quality of care is the establishment of standardised procedures and protocols that reduce variability and increase effectiveness when implemented correctly. Observations have shown that the compliance to disinfection procedures tends to be low

particularly as to preparation time and dry time, both essential to the efficacy and safety of the procedure.^{153 154 155}

Reducing manipulations simplifies the procedure and improves compliance.^{156 157 158}

Reducing waste

The use of an all in one system reduces the need for auxiliary materials (gauze, instruments, swabs). This material may in some cases represent a cost of the same order of magnitude as the antiseptic itself.¹⁵⁹

VIII. RECOMMENDATIONS

RECOMMENDATION 1:

Open a new phase in the prevention of healthcare associated infections by making the fight against the most common healthcare associated infections, and in particular against surgical site infections and catheter-related infections, a priority in the political agenda on patient safety.

RECOMMENDATION 2:

Promote EU-level guidelines or recommendations on skin antiseptics which specifically address surgical site infections, catheter-related bloodstream infections and blood culture contamination as the leading contributing factors to healthcare-associated infections.

RECOMMENDATION 3:

Promote skin antiseptics in the framework of any relevant ongoing and upcoming political initiative on Antimicrobial Resistance and in particular in the European Commission 'Action Plan Against the rising threats from Antimicrobial Resistance: Road Map', so as to reduce the unnecessary use of antibiotics due to blood culture contamination and decrease the consumption of antibiotics by reducing surgical site infections and Catheter-Related Infections (CRIs).

RECOMMENDATION 4:

Promote EU guidelines/recommendations to clarify and promote a harmonised approach across the EU on the classification of skin disinfectants before surgery and insertion.

RECOMMENDATION 5:

Promote EU guidelines on skin antiseptics as a relevant factor for patient safety and the prevention of HAI's, recommending the use of sterile 2% Chlorhexidine in 70% Isopropyl Alcohol (in the absence of specific contraindications) as the safest and most efficient solution for the prevention of healthcare-associated infections.

RECOMMENDATION 6:

Consider the method of application of the skin antiseptic in the guidelines on skin antiseptics, with a special focus on single-use applicators.

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