

Peer Review File

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Reviewer A

Comment 1: This manuscript is hard to follow. Too much information. The case report should be short. The feeling is that the manuscript has not been through any proofreading.

Throughout the manuscript the name, *S. lugdunensis* is several times spelled wrong.

Reply 1: The authors would like to thank and apologize to the reviewer regarding the manuscript hard to follow with too much information. The patient described had a very complicated course during her illness. The patient had significant number of treatments in the CCU, followed with multiple major operations and a prolonged ICU stay before her demise. The authors will attempt to streamline further the manuscript and make the appropriate spelling errors as stated by the reviewer.

Changes in text: Please see revised manuscript with modifications in red.

Comment 2: Line 22-23 and 65. The information about any vaccination in the case does not give any valuable information. Since she had the symptoms prior to the vaccination this only confuses the patient history. Skip it.

Reply 2: The authors agree with reviewer the information on any vaccination does not provide any more valuable information.

Changes in text: The vaccination information deleted. Line 42-46 and line 82-85.

Comment 3: Line 37-38, Key words and, 263, 266, 269, 270, 282 Table 1., *Staphylococcus lugdunensis* without capital L.

Reply 3: The authors appreciate the reviewer's input on the capital letter.

Change in text: Line 59-60, 265, 269, 270 and Table 1 title corrected.

Comment 4: Line 96 *S. lugdunensis*, Check the spelling! Susceptible to oxacillin/cloxacillin and Septra (What is this? This is a brand name, please correct)

Reply 4: The authors appreciate reviewer's input and made the appropriate change. Oxacillin/cloxacillin are generic name and Septra is the trade name.

Change in text: Line 141-142 corrected. Oxacillin (generic name) with its trade name Bactocill and Cloxacillin (generic name) with its trade names are: Cloxapen®, Orbenin®, Tegopen®. Septra (trade name)'s generic name is Trimethoprim/Sulfamethoxazole. The three drugs will be in its generic name, line 109.

Comment 5: There is no date when the trans-oesophageal echocardiogram /TEE, was performed! Please add that information

Reply 5: The authors agree with the reviewer the date to be added to the TEE performed.

Changes in text: Date 18 Jan 2020 TEE performed added on Line 132-133.

Comment 6: 178, 226 ,spelling of *S. lugdunensis*!

Reply 6: The authors appreciate the reviewer check on the spelling of *S. lugdunensis* which is to be corrected.

Changes in text: Line 100 and 232 with corrected spelling.

Comment 7: 193 I do not think that all agree that *S. aureus* is a beneficial bacterium on the skin.

Reply 7: The authors agree with the reviewer the statement to be modified. In normal healthy skin-barrier the colonized organism mentioned may be protective and it is only when the skin barrier is damaged then the mentioned organism can become harmful.

Change in text: The word beneficial deleted and sentence revised line 84-90.

Comment 8: 209 – 211 Staphylococcus organism, rather staphylococci and coagulase-negative/positive staphylococci

Reply 8: The authors agree with the reviewer in changing the grammar.

Change in text: Line 218-221 the word “rather” added to the statement.

Comment 9: 209-224 A rather messy information that has to be shortened and clarified. As in line 223 “including include patients with diabetes”.

Reply 9: The authors agree with the reviewed the information provided Line 209-224 needs to be modified.

Change in text: Line 218-231 shortened and clarified. The word on line 218 include deleted. “Staphylococcus organisms rather coagulase-positive staphylococcus (CoPS), such as *S. aureus* that colonizes nearly 30% of the human skin and mucosa; or coagulase-negative staphylococcus (CoNS), such as *Staphylococcus epidermidis* (*S. epidermidis*) that colonizes nearly all human skin (9). This virulent bacterium produces a wide range of toxins implicated in the etiology of specific clinical manifestations, such as skin and soft tissue infection, necrotizing pneumonia and toxic shock syndrome (13). But culture positive CoNS, often indicating as contaminants and absence of virulence factors (13). However, the emergence of nosocomial and community pathogens with CoNS associated with the use of indwelling or implanted foreign bodies has become a key source of endogenous systemic infection (14) via sites, including blood, cardiac tissues, central nervous system and urinary tract (15). Particularly, CoNS can also act as a pathogen in the elderly and immunocompromised, including patients with diabetes, renal failure, or patients receiving chemotherapy (15). Our patient’s risk factor for CoNS infection is her age. She did not have any significant medical ailments, although had breast cancer 21 years ago treated with lumpectomy and radiation but clinically she was not immunocompromised.”

Comment 10: 226. *S. lugdunensis* is not a group of CoNS but one species included in the larger group of CoNS.

Reply 10: The authors agree with the reviewer *S. lugdunensis* is one of the species of CoNS.

Comment in text: Line 232 text change to “*S. lugdunensis* one of CoNS specie organism initially described in 1988.....”

Comment 11: 231. *S. lugdunensis* in Italic!

Reply 11: The authors agree with the reviewer the *S. lugdunensis* be in Italic.

Comment in text: *S. lugdunensis* in italic line 237-238.

Reviewer B

Comment 1: (1) Background: More background information is required. The authors should state what is known and unknown; why the case report is unique and what it adds to existing

literature in the subsection. The unique point should be clearly specified like the statement in the conclusion - “This is the first reported case of *S. lugdunensis* endocarditis induced by excessive use of ABHD without moisturizer affecting the hand barrier function”.

(2) Case Description: The following detailed information should be provided in this subsection, including the patient’s main history, the drug, dosage, frequency and duration of the antibiotics therapy.

Reply 1: The authors agree with the reviewer and added more background information.

Change in text:

Line 38-43 Background: WHO and national disease control agencies emphasized the importance of hand hygiene to reduce the spread of the virus during COVID-19 pandemic to curb the spread of the virus coupled with vaccination. Alcohol-based hand sanitizer (ABHS) formulation is effective to reduce or eliminate bacterial or viral load, and commonly applied in the form of hand rub rinses, gel and foam, but it may impair skin barrier integrity and function, increasing the risk of hand dermatitis resulting local and/or systemic infections.

Line 44-54 Case Description: A 75-year-old woman used ABHS excessively without skin moisturizer resulted bilateral dry skin-crack hands. 2 weeks prior to hospital admission, she experienced progressive generalized fatigue, shortness of breath with moderate exertion, bilateral lower leg edema, orthopnea and paroxysmal nocturnal dyspnea associated with fever and chills. She was diagnosed with *Staphylococcus lugdunensis* (*S. lugdunensis*) aortic and mitral valve endocarditis. Intravenous antibiotics coupled with urgent cardiac surgery to replace the aortic valve, debridement and reconstruction of the left ventricular outflow track followed by a complex mitral valve repair. Her post-operative course complicated by requiring intra-aortic balloon pump (IABP), VV-ECMO and Continuous Venous-Venous Hemodialysis (CVVHD). Despite decannulation of all three mechanical supports, the patient continued to have multiple ICU related medical and surgical complications, resulted her mortality.

Comment 2: 2. Keywords. Please add “case report” as a key word in this manuscript.

Reply 2: The authors agree with the reviewer to add case report to keyword.

Changes in text:

Line 59-60 Keywords:

Case report, Alcohol based hand sanitizer (ABHS), COVID-19, *Staphylococcus lugdunensis*, Endocarditis

Comment 3:

Introduction

- (1) The information in the Introduction is too little. Please kindly reorganize the content according to the “Author Instruction” to provide a more informative Introduction. In brief, Introduction should be structured in three parts: a) Background, b) Rationale and knowledge gap, c) Objective.
- (2) Meanwhile, the contents of the first, second and third paragraphs of the current Discussion section are not for discussion, but should be included in the Introduction.
- (3) Please also highlight the unique point of this manuscript in the Introduction. This should be supported by evidence based on comparison with similar cases (i.e., give a brief summary of the induced reasons in similar cases with *S. lugdunensis* endocarditis).

Reply 3:

- (1) The authors agree with the reviewer Introduction expanded.
- (2) The authors agree with the reviewer the content of the first, second and third paragraph in current Discussion be included in the Introduction
- (3) The authors agree with reviewers. This is the first reported case of excessive hand hygiene with ABHS causing SL endocarditis. Also the authors did a through literature review searching SL endocarditis due to post procedure as described in the Discussion Table 1.

Changes in text:

Line 66-104 modified introduction as recommended.

“The COVID-19 pandemic posed unprecedented challenge to public health around the world. Universal vaccination is an effective measure to combat COVID-19, but public health infection control measures such as hand hygiene and mask for contact and respiratory control to prevent the spread of the virus has been the primary focus. The WHO and national disease control agencies emphasized the importance of hand hygiene to reduce the spread of the virus by frequent washing with soap and water after going to the bathroom, before eating or after coughing, sneezing or blowing one’s nose (1). When soap and water are not available sanitizing of non-visibly soiled hands with at least 60% alcohol-based agent is recommended (2). Each Alcohol based hand sanitizer (ABHS) formulation maybe effective to reduce or eliminate bacterial or viral load, it is commonly applied in the form of hand rub rinses, gel and foam (3), but it may impair skin barrier integrity and function, increasing the risk of hand dermatitis resulting local and/or systemic infections (4).

ABHS contains the alcohol ingredients isopropanol, ethanol or n-propanol or a mixture of the three agents (5). These ingredients have the anti-microbial ability to denature and coagulate proteins, thus causes the microbes to lose its protective lipid membrane, inhibition of its metabolism and induce lysis of the viral particle (1). The Center for Disease Control and Prevention recommends acceptable formulations to contain 80% (percent volume/volume) ethanol or 75% (percent volume/volume) isopropyl alcohol (2).

Our skin barrier contains a large proportion of stratum corneum, which composed of keratin and lipids (6). Under healthy conditions, the skin barrier colonized with various bacteria such as *Staphylococcus epidermis*, *Staphylococcus aureus*, *Micrococcus spp.*, *Propionibacterium spp.* and *Corynebacterium spp.* which are not harmful to the human host (7,8). These bacteria may help to prevent the colonization of other pathogenic microbes by either competing with them for nutrients or stimulating the skin's defense system and under exhibits low pathogenicity under normal healthy conditions (3). However, when the epidermis micro-environment is disrupted, by prolonged antibiotics use, frequent hand washing with alkaline soap and detergents, water with extreme temperatures, low humidity, repeated glove use, working in wet environment and rough paper towels these protective organisms can become virulent (9). A strict and frequent hand hygiene utilizing lipid-emulsifying detergents and lipid-dissolving alcohols can cause an acute loss of skin surface lipids, which depletes the corneum stratum protein, thereby decrease corneocyte cohesion and reduction of corneum water binding-capacity (10). The degraded skin barrier can increase transdermal water loss (TEWL), permits epidermal penetration of irritants, allergens and microbes, which propagates an inflammatory response resulting in hand dermatitis, which may contribute to local or systemic infection (10).

We report the first case of a patient developed *S. lugdunensis* induced aortic and mitral valve endocarditis, with excessive use of ABHS without moisturizer, compromised hand skin integrity. The patient required operative valves repair, VV-ECMO, dialysis and an IABP while post-operation in the Intensive Care Unit (ICU) for refractory hypoxia from severe congestive heart failure.”

Comment 4: Case presentation

The detailed information of the received treatment should be clearly clarified (e.g., loading clopidogrel, aspirin, ceftriaxone and so on). Detailed information includes the dosage, strength, duration.

Reply 4: The authors agree with the reviewer the full descriptions to the medications

Changes in text: line 126-128 treatment clarified.

Comment 5: Timeline

We suggest the authors adding a timeline. The timeline should present relevant events in the patient's history in chronological order in a figure or table, enabling the core elements of the case report standing alone. Please see some examples from our sister journals:

Reply 5: The authors agree with the reviewer a time line figure added

Change in text: Line 201-Figure 3 added on timeline of relevant clinical events for this case report

Comment 6: Discussion

Similarly, Discussion is structured in five parts: a) Key Findings, b) Strengths and limitations, c) Comparison with similar researches, d) Explanations of findings, e) Implications and actions needed.

Reply 6: The topic of interested as recommended by the reviewer applied in various section of the discussion.

Change in text: Please review the discussion section and highlighted in red.

Comment 7: Figures and Tables

(1) Please just reserve one title for the Figures.

(2) Whether "28 X 10 mm" should be revised to "21 X 9 mm" in Figure 1?

(3) The full names of all abbreviations should be provided in the footnote of Table 1, for example, the full name of AVR seems not to be provided.

Reply 7:

(1) The authors will reserve one title per figure

(2) "28 X 10 mm" should be revised to "21 X 9 mm" in Figure 1 – revised

(3) Abbreviations to be in the footnotes.

Change in text:

(1) Figure 1A, B, C and D separated into 4 independent figures

(2) The measurements revised

(3) Abbreviation for each figure applies as footnotes

Comment 8: There are some content showing duplication with previously published articles (e.g. line 183-189, line 192-197). Please paraphrase instead of direct using the same wording or simple word switching

Reply 8: The authors agree with the reviewer.

Change in text: Line 78-83- ABHS contains the alcohol ingredients isopropanol, ethanol or n-propanol or a mixture of the three agents (5). These ingredients have the anti-microbial ability to denature and coagulate proteins, thus causes the microbes to lose its protective lipid membrane, inhibition of its metabolism and induce lysis of the viral particle (1). The Center for Disease Control and Prevention recommends acceptable formulations to containe 80% (percent volume/volume) ethanol or 75% (percent volume/volume) isopropyl alcohol (2).

Line 84-90- Our skin barrier contains a large proportion of stratum corneum, which composed of keratin and lipids (6). Under healthy conditions, the skin barrier colonized with various bacteria such as Staphylococcus epidermis, Staphylococcus aureus, Micrococcus spp., Propionibacterium spp. and Corynebacterium spp. which are not harmful to the human host (7,8). These bacteria may help to prevent the colonization of other pathogenic microbes by either competing with them for nutrients or stimulating the skin's defense system and under exhibits low pathogenicity under normal healthy conditions (3).