The interplay between acute bacterial skin and skin structure infections and depression: a vicious circle of major clinical importance

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Purpose of review
Previous studies suggest an association between depression and increased risk of various type of infections, including acute bacterial skin and skin structure infections (ABSSSI). Here, we review the latest advancement in our understanding of immunity in patients with depression and its relevance to disease management and diagnosis, with a special focus on patients suffering from ABSSSI.

Recent findings
Recent studies have highlighted the role of hypothalamic–pituitary–adrenal axis, neuro-endocrine stress signaling pathways and behavioral attitudes (substance abuse and homelessness) in the pathogenesis of infections in depressed patients. Furthermore, acute bacterial infections, in turn, have emerged as a possible risk for depression development because of different mechanisms including antibiotic-driven changes in the microbiota.

Summary
Recent evidences have emphasized the threat that comanagement of depression and infection pose to infectious disease physician and psychiatrist. Depressed patients with ABSSSI must be closely monitored for drug side-effects, drug–drug interactions, toxicity, and adequate compliance. New management strategies including new long-acting antibiotics (e.g., dalbavancin) are welcome.

Keywords
acute bacterial skin and skin structure infections, dalbavancin, depression, drug toxicity, drug–drug interactions

INTRODUCTION

By 2030, the World Health Organization projects that depression will be the most common cause of disability in high-income countries [1,2]. Up to 32% of the adults are expected to experience at least one depressive episode during their lifetime [3,4], which will have a negative impact on their quality of life [5], relationship and employment [6]. Moreover, recent reports have found depression to be associated with an increased risk of the onset of physical diseases [7], including autoimmune disease [8], cardiovascular disease [9] as well as a wide range of bacterial infections [10,11,12▪▪].

In particular, the link between infections and depression seems to be complex with at least three factors influencing this association [13–15]. First, drawing on the most recent evidence, depression by itself may be related to increased risk of infection development, estimated to be 60% higher compared with the same risk for the general population [10]. Second, a diagnosis of infection may directly lead to depression, especially in older hospitalized patients who are at greater risk of failing to regain baseline functional status [16–18]. Third, both diseases share

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KEY POINTS

- Recent evidences suggest an association between depression and increased risk of various type of infections, including ABSSSI.
- Comanagement of depression and ABSSSI pose serious challenges to infectious disease physician and psychiatrist because of drug side-effects, drug–drug interactions, toxicity and inadequate compliance.
- New management strategies including new long-acting antibiotics (e.g., dalbavancin) are welcome.

some predisposing conditions including substance abuse and homelessness [13–15].

Among the different types, acute bacterial skin and skin structure infections (ABSSSI) represent by far the most recurring infection in both ambulatory and hospital setting [19], with a dramatically increase in incidence in recent years [20]. Consequently, patients with ABSSSI may potentially suffer from the highest burden of depression's comorbidities in absolute terms; for example, 170 cases of skin infections in patients with depression were identified between 1995 and 2012 in a prospective population-based study including 142 169 depressed individuals, compared with only 17 and 11 patients with gastrointestinal or central nervous system infection [10].

In this review, we consider our current understanding of inflammatory, immune and behavioral changes observed in depression and infections, with a special focus on patients suffering from ABSSSI. We also try to offer a multidisciplinary approach that, by integrating the expertise of different disciplines (infectious disease, psychiatry, primary care) can improve compliance, reduce side-effects and, ultimately, achieve the best functioning and quality of life for depressed patients with ABSSSI.

DEFINITION OF DEPRESSION

The term 'depression' has a wide spectrum of meaning, ranging from transient feeling of flat mood to serious clinical syndromes, that can be severe and disabling [21]. Depression is usually presented as a single or recurrent depressive episode characterized by depressed mood, anhedonia, sleep disturbance, change in appetite or weight, loss of interest, low energy, poor concentration, and recurrent thoughts of death or suicide. It can also present as a milder or persistent condition which does not fulfill the full criteria of a depressive episode, but that still, contributes to a significant burden for the patients and for their caregivers as well [20]. In addition, patients with infections may suffer from a depression type ('depressive disorder due to other medical condition') which fully or partially fulfills the criteria of major depressive episode, or from depression in the context of neurocognitive disorders (e.g., dementias, Parkinson disease), in which the presence of a depressive episode or depressive symptoms is highly prevalent [22–25].

EPIDEMIOLOGY AND CLINICAL MANIFESTATION OF INFECTIONS IN PATIENTS WITH DEPRESSION

There is evidence in the literature that a diagnosis of depression is associated with a subsequent risk of infectious disease, including ABSSSI (Table 1). An impressive Danish registry of first hospital contacts comprising 976 398 individuals identified 142 169 patients with diagnosis of primary depression. Compared with patients without depression, onset of depression was associated with substantial infection risk (adjusted relative risk 1.67, $P < 0.0001$), that remained relatively consistent over an 11-year period [10]. In this study, ABSSSI were among the most common types of infections associated with depression with adjusted relative risk of 1.46 compared with 1.19 for gastrointestinal infections, 0.91 for central nervous system infections, and 1.58 for respiratory infections. More interestingly, it was described that the relationship between the two conditions showed a positive correlation, whereby patients with more depressive episodes were at higher risk of developing infections [10]. Similar results were also reported in a prospective longitudinal cohort study previously conducted in the United States, in which a history of depressive symptoms was reported in 28% of patients that were developing severe sepsis [26].

Depression has also been reported as a significant risk factor for the development of different infections, including post knee arthroscopy infections [27], *Clostridioides difficile* infection [28], respiratory tract infections [29], peritonitis [30], bloodstream infections [11], or ventricular assistance device infections [31]. As for ABSSSI, in a recent case-control study of patients undergoing cardiothoracic surgery, history of depression was associated with increased risk of developing sternal wound infection. In this study, the association between depression and risk of infection (adjusted odds ratio 2.4; 95% CI 1.2–4.7; $P = 0.01$) was stronger than that observed with any other medical morbidity (i.e., obesity, heart failure), and *Staphylococcus aureus* was the most common isolated pathogen [12▪▪]. Other authors also suggested that a history

Table 1. Evidence supporting the interplay between depression and ABSSSI

Reference	Country	Period of study	Design	Number of patients with depression and comparators	Main findings
[32]	USA	Not reported	Longitudinal study including 67 women after coronary artery bypass surgery	39 nondepressed woman versus 28 women with minor or major depression	Compared with nondepressed women (0.03 ± 0.17), women with minor (0.17 ± 0.58), or major depression (0.62 ± 0.96) had more all-cause infections
[55]	USA	1998–2006	Population-based cohort of older adults	471 patients surviving at least one episode of severe sepsis. No comparator groups were available	Point prevalence of substantial depressive symptoms was 28% at a median of 1.2 years before sepsis and remained 28% at a median of 0.9 years after sepsis
[36]	Canada	2003–2007	Retrospective observational study	390 geriatric patients with an underlying psychiatric disorder No comparator groups were available	85 out of 390 had an infection at the time of hospital admission. No control/comparator group was available
[53]	Canada	1995–2009	Retrospective cross-sectional design	To assess the frequency of psychiatric disorders in bacterial skin infections (*N* 18 734) versus malignant and benign cutaneous neoplasms ($N = 8376$)	Skin infections were more commonly (odds ratio 3.03, 95% CI 1.58–5.82) associated with a psychiatric disorder (not reported incidence)
[10]	Denmark	1995–2012	Prospective nationwide register-based study	142 169 depressed patients compared with 834 229 nondepressed individuals	Incidence rates of infection episode per 100 000 person-years 84.4 episodes in depression group versus 54.7 in the control group
[12▪▪]	USA	2007–2012	Retrospective 1:2 case-control study	129 patients developing sternal SWI after cardiothoracic surgery were matched with 258 controls without SWI	Depression symptoms were observed in 28/129 (21.7%) case patients versus 29/258 controls (11.2%)

ABSSSI, Acute bacterial skin and skin structure infections; CI, confidence interval; SWI, sternal wound infection.

of depression may pose a significant risk for developing surgical-site infections [32,33].

As for clinical presentation, infections among psychiatric patients are not easily identified by treating physicians and health workers [34,35]. This was observed in a Canadian retrospective study in which the prevalence rate of infections among psychiatric inpatients on admission was about 20%, with the commonest ones being urinary tract infections and ABSSSI [36]. In this study, the diagnosis of infection was initially unidentified in many cases as the disease onset was associated with clinical manifestations of the psychiatric disorder or a delirium because of another cause. Therefore, when a patient with a psychiatric disorder presents with symptoms of agitation, motor slowdown, or cognitive impairment, infection is one highly plausible underlying cause.

PATHOGENESIS OF INFECTIONS IN PATIENTS WITH DEPRESSION

The impact of depression on infections may be directly related to two factors: the immunological changes observed in patients with depression and the individual symptoms of depression that may have a significant predisposing role. Both mechanisms are not only associated with complications in the late stage of the disease but may also speed up the interplay between infection and depression in the initial phases.

Several studies indicate that the association between depression and the risk of infections may be mediated by the dysfunction of the hypothalamic–pituitary–adrenal axis that results in high levels of glucocorticoids, observed in many patients with depression [37]. The effects of glucocorticoids on immune functions include a change in the trafficking leucocytes, diminished function of natural killer cells and Th1 lymphocytes, altered inflammatory cytokine production, and reduced immunoglobulin synthesis, as well as impairment in delayed hypersensitivity reactions [38,39]. The high levels of corticosteroids are also considered to be associated with an increased risk of glucose intolerance and diabetes [38,39], which is also a risk factor for developing infections, including ABSSSI [40].

Moreover, by triggering neuro-endocrine stress signaling pathways, depression may affect the

steering of immunological gene expression [41], thus impairing the immune system function and finally contributing to an increasing susceptibility to infection [41–43]. Other hormones and neurotransmitters such as serotonin, epinephrine, dopamine, and acetylcholine are relevant in the pathophysiology of depression and may also affect immune regulation [44].

Individual symptoms of depression may also have a direct role in promoting infections. Change in appetite or weight is frequently observed in depression, whereas both underweight and obese individuals are at increased risk of ABSSSI and recurrent cellulitis [45]. Sleep is considered an important modulator of the immune response and clinical studies described a positive association between sleep deprivation and risk of infections [46,47]. Yet, experimental studies in animals have proven a relationship between the duration of sleep and infection outcome [48,49].

Finally, depression is indirectly related to infections through several common risk factors. For example, intravenous drug use is recognized as a common risk factor for both depression and infections [50] (i.e. endocarditis, acute bacterial skin, and soft tissue infections). Furthermore, alcohol abuse, homelessness, poor adherence to medication, and poverty have all been separately linked to both depression and infection [13–15].

DEPRESSION IN PATIENTS WITH INFECTION

The interplay between depression and infections appears to be a self-perpetuating circle, where acute bacterial infections, in turn, may increase the risk of depression symptoms [51,52].

To the best of our knowledge, the incidence rate of depression after acute infection is not well established mainly because large prospective longitudinal studies assessing this issue have not been performed yet. However, in a recent study analyzing the frequency of psychiatric morbidity in patients with skin diseases, Gupta *et al.* [53] found that depression was diagnosed in almost 20% of the patients with ABSSSI. Several reasons may be mentioned including severity and type of infections, along with biological and social factors [54].

Patients with severe sepsis are exposed to enormous stressors such as pain, respiratory insufficiency, surgery (e.g., amputation) and need for mechanical ventilation [17,55]. All these aspects, affecting physical and cognitive activity, can cause somatic dysfunction which can trigger and exacerbate the occurrence or worsening of depression [17,55]. Moreover, patients with serious infection may require a long hospitalization in which potential complications, increasing dependence by other people and decline in functional status could increase the risk of developing depression [56–59]. Even the risk of suicide increases in patients with infectious diseases, showing a synergic effect of medical illnesses and underlying depressive symptoms on this risk, particularly in older patients and in patients with poor adherence to antidepressant treatment, an occurrence particularly frequent in patients with psychiatric and organic comorbidity [60]. Regarding this aspect, efforts should be made to implement screening tools for detecting patients admitted for serious infections with higher risk to develop depressive symptoms during and after hospitalization.

The need for contact isolation has also been advocated to explain the increased symptoms of depression observed in patients with infection [61]. Regarding ABSSSI, most cases are because of multidrug-resistant organisms such as methicillin-resistant *S. aureus* [62] that require the use of contact isolation to prevent patient-to-patient transmission [63]. Contact precautions have been associated with a 40% greater likelihood of receiving a diagnosis of depression, even after adjusting for potential confounders [61]. Such effect is partially explained by the uncertainty and loss of control that ultimately stems from isolation itself. Patients' education and a good communication with them may be beneficial to reduce depressive symptoms related to patient isolation [64].

Fear of diagnosis, disability, activity restriction and decreased social participation may also cause depression in older individuals with ABSSSI [65]. In addition, it is also likely that the occurrence of depression in patients with infections may be mediated by pain [66]. Previous studies have shown that patients experiencing severe pain are 3–5 times more likely to develop depressive symptoms in comparison to those without pain [66]. Pain seems to be the most distressing symptoms universally experienced in patients with ABSSSI [67] and the prominence of pain symptoms can also interfere with the recognition of depression in primary care [68].

As for biological factors, a number of studies currently support the hypothesis that infections can play a role in the pathogenesis of psychiatric disorders through an increase in the levels of ongoing inflammation and proinflammatory cytokines [69], such as interleukins or tumor necrosis factor (TNF)-α that may contribute to central nervous system changes and microglial remodeling [70]. Finally, another very attractive and fashionable theory considers depression as a consequence of antibiotic-driven changes in the microbiota. Although the effect of antibiotic exposure on the

gut microbiota is difficult to predict [71], there is evidence suggesting that antibiotics disruption of the gut microbiome leads to lasting effects outside the gastrointestinal system through bidirectional communication with different systems, including the central nervous systems (gut–brain axis) [72,73]. For example, in a recent case-control study performed in England, Lurie *et al.* [74] found that recurrent antibiotic exposure was associated with higher risk for depression for all antibiotic groups, with an adjusted odd-ratio up to 1.40 and 1.56 for penicillins and quinolones, respectively. Similar results were also observed in a rat model in which behavior changes were observed following dysbiosis after antibiotic administration [75]. Interestingly, in such study behavior changes disappeared once the gut microbiome returned to basal conditions, thus further supporting the possible influence of gut on the brain [75]. Despite these interesting findings, future researches are needed to better clarify the role of gut–brain axis on depressive symptoms development as well as the impact of the gut on the microbiota induced by specific antibiotics administered.

TREATING INFECTIONS IN PATIENTS WITH DEPRESSION

The frequent comorbidity of infections and depression implies a high probability that an infectious disease doctor will treat infected patients with a diagnosed or undiagnosed depression. Similarly, psychiatrists are likely to treat depressive patients with coexisting infection. Thus, both infectious disease physicians and psychiatrists need to be familiar with problems that can arise from medical management of both diseases, so that they are able to offer a multidisciplinary strategy that guarantees the best therapy while minimizing the risk of adverse events and drug–drug interactions. Indeed, patients should be listened in their narrative of illness, and not only merely treated with target organ disease remedy. Patient's quality of life is positively associated with a holistic caring approach, and this is feasible with a multidisciplinary approach [76,77].

Once an ABSSSI has been diagnosed in a patient with depression, administering an adequate antibiotic treatment is paramount [78]. To date, the most appropriate therapy for depressed patients with ABSSSI is still an unresolved issue, and there are no specific recommendations for antibiotic treatment in depressed patients beyond the usual clinical guidelines [15,79].

Current guidelines of the Infectious Disease Society of America divide ABSSSI treatment according to nonpurulent (cellulitis and erysipelas) and purulent infections (abscesses) [15]. The majority of these infections are caused by β-lactam-resistant microorganisms [80]. In a large survey conducted between November 2014 and December 2016 among 1027 patients with ABSSSI, 52.1% were infected by gram-positive cocci, 20.5% by gram-negative bacteria, and 27.3% by both gram-positive and gram-negative microorganisms. The overall level of resistance of gram-positive cocci to methicillin was 57.3% whereas the level of resistance of gram-negative pathogens to amoxicillin-clavulanate exceeded 50% [81]. To this end, vancomycin, linezolid, and daptomycin are usually considered the primary treatment option for the empirical or definitive treatment of ABSSSI, including those episodes caused by methicillin-resistant *S. aureus* [80,82]. In cases in which a severe polymicrobial infection is suspected, piperacillin-tazobactam or fluoroquinolone therapy should be included in the regimen. Lastly, treatment with either doxycycline, clindamycin, or trimethoprim-sulfamethoxazole is considered a viable treatment option in cases of moderate purulent infections [15].

Despite the fact that different antibiotics are similar in terms of clinical efficacy, certain drugs may be preferred for treating depressed patients with ABSSSI, as some of them pose potential drawbacks such as drug–drug interactions, adverse drug reactions, intolerance, and difficult therapeutic compliance with consequent clinical and microbiological failure. Considering the former, the occurrence of significant drug–drug interactions between antibiotics and antidepressants is frequent (Table 2). For example, linezolid is a mild reversible nonselective monoamine oxidase inhibitors (MAO) inhibitor activity that, interacting with antidepressant drugs, may consistently increase the risk of developing a serotoninergic syndrome [83]. This syndrome, occurring in 3–4% of all patients under concomitant psychiatric and linezolid treatment, is usually characterized by cognitive and behavioral (e.g., confusion, agitation), autonomic (e.g., fever, diaphoresis, tachycardia), and neurological (e.g., myoclonus, rigidity) symptoms and is a manifestation of overactivation of peripheral and central 5-HT1A or 5-HT2A receptors [84–87]. As for fluoroquinolones, there is no evidence of any significant interactions with antidepressant medications in term of drug–drug interactions. However, because fluoroquinolones have been associated with increased QT interval, particular attention should be taken when administering it in patients receiving other agents which also have the same effect (i.e., citalopram or escitalopram) [88,89]. In such circumstances, a strict monitor of QT interval is warranted especially in cardiopathic patients in which QT interval is borderline (450 ms for men and 470 ms for a woman).

Table 2. Dose ranges, advantages, and antidepressant drug interactions of commonly used antibiotic medications for acute bacterial skin and soft structure treatment

Drug	Usual dose	Activity against MRSA	Need for renal adjustment	Need for hepatic adjustment	Potential problems with patients' compliance[a]	CNS adverse effects (% average incidence)	Interactions with antidepressants
Minocycline	100 mg q12 h	Limited	No	No	Yes. Oral administration	Vestibular symptoms [125,126] Pseudotumor cerebri (8–15%) [125–127]	Not reported
TMP-SFX	160/800 mg q12 h	Yes	Yes	No	Yes. Oral administration	Headache, confusion, delirium, aseptic meningitis (8–83% of the patients depending on underlying disease and drug dosage) [128–131]	Nortriptyline, desipramine, amitryptiline, doxepin, fluoxetine, imipramine, trazodone, clomipramine, sertraline, venlafaxine, mirtazapine, citalopram
Doxycycline	100 mg q12 h	Limited	No	No	Yes. Oral administration	Headache, dizziness, vertigo (5–15%) [127]	Not reported
Clindamycin	300–600 mg q8 h	Limited	No	Maybe required	Yes. Oral administration	Headache, nausea, vomiting, taste disturbing (anectodical cases) [90]	Not reported
Linezolid	600 mg q12 h	Yes	Reports of drug accumulation in patients requiring chronic hemodialysis	No	Yes. Oral administration	Headache (6.0%), dizziness (2%), insomnia (1%), neuropathy (0.38%) [132,133]	Nortriptyline, desipramine, amitriptyline, buproprion, doxepin, fluoxetine, imipramine, trazodone, clomipramine, sertraline, paroxetine, venlafaxine, fluvoxamine, nefazodone, mirtazapine, citalopram
Tedizolid	200 mg q24 h	Yes	No	No	Yes. Oral administration	Headache (6.0%), dizziness (1.8%) [132]	Not reported
Vancomycin	15 mg/kg IV q 12 h	Yes	Yes	No	Only intravenous formulations	Ototoxicity (12%) [134]; dizziness, vertigo and tinnitus (rarely reported) [90]	Not reported
Tigecycline	100 mg IV as a single dose, then 50 mg IV q12 h	Yes	No	Yes	Only intravenous formulations	Headache (5.9%), dizziness (3.5%), and insomnia (2.3%) [135]	Not reported
Ceftaroline	600 mg q12 h	Yes	Yes	No	Only intravenous formulations	Headache (3.4%) and dizziness (2%) [136]	Not reported
Dalbavancin	1500 mg single dose or 1000 mg once followed by 500 mg after 1 week	Yes	Only in patients with renal failure not undergoing hemodialysis	No	Only intravenous formulations Limited concern because of single shot administration	Headache (4.7%) and insomnia (1.5%) [137]	Not reported

TMP-SFX, Trimethoprim/sulfamethoxazole.
[a]The evaluation for such problem is the opinion of the experts writing this review.

Another potential obstacle to the successful treatment of ABSSSI in patients with depression is the potential psychiatric and neurological adverse events of antibiotics [90]. Although these effects have not been specifically described in patients treated for ABSSSI, fluoroquinolones [91], sulfonamides [92], and carbapenems [93,94] have all been associated with depression, psychosis, delirium, and suicidal ideation [95]. The majority of literature regarding to these aspects refers to fluoroquinolones and sulfonamides. Central nervous system events have been reported in 1–3.3% of patients taking a fluoroquinolone [91,96], with confusion (51%), hallucinations (27%), agitation (13%), and delusion being the most frequently psychiatric effects observed [96]. Samyde *et al.* [97] also found 608 reports of suicidal behavior correlated with fluoroquinolones therapy, 97 of which completed the suicide. Of importance, fluoroquinolones have been associated, with delayed effects, to persistent or progressive psychiatric adverse events, even when fluoroquinolones have been discontinued [98]. As for trimethoprim/sulfamethoxazole (TMP-SFX), drug-induced psychosis may be dose dependent and has been mainly reported in immunosuppressed patients with incidence rates up to 12% [92,99].

As for other adverse drug reactions, careful follow-up should be performed when vancomycin is administered because of the potential risk of acute kidney injury, especially in patients receiving combination treatment with piperacillin-tazobactam [100] or with other nephrotoxic drugs, like diuretics [101]. Daptomycin is usually considered a viable alternative to vancomycin [102], but elevation in serum creatine phosphokinase (CPK) should be monitored, especially in patients also receiving statin [103]. Linezolid reveal specific reversible myelotoxicity and irreversible neurotoxicity, which can be clinically relevant and should be considered as part of benefit-risk evaluation, when a regimen including this bacteriostatic drug is initiated [104].

ADHERENCE TO TREATMENT IN PATIENTS WITH ACUTE BACTERIAL SKIN AND SKIN STRUCTURE INFECTIONS AND DEPRESSION

Another issue that should be considered for an adequate treatment of patients with depression is the inherent difficulties of oral drug delivery modes. Previous studies have shown that depression has a profound impact on compliance to oral therapy, especially when the dose regimen is more complex and multiple-day oral therapies are prescribed [105,106]. Moreover, patients taking antidepressants tend to have higher rates of medication noncompliance than other patient populations [107]. Reports have demonstrated a positive association between medication noncompliance and hospital admissions and readmissions [108]. Although compliance to treatment is likely not to be a major concern during hospitalization, it could affect depressed individuals while in the community [107]. Those patients may consequently not attend to follow-up visit or take treatment incorrectly [109]. Considering delivery modes, first-line antibiotics for ABSSSI (i.e., vancomycin or daptomycin) require an intravenous administration with prolonged hospitalization [110], whereas oral administration of linezolid has also been associated with potential problems of compliance, even in patients with no psychiatric disease [111]. Accordingly, the problem of nonadherence to medical therapy in patients with depression still persists [112,113,114], despite different approaches have been applied.

A NEW APPROACH FOR THE MANAGEMENT OF DEPRESSED PATIENTS WITH ACUTE BACTERIAL SKIN AND SKIN STRUCTURE INFECTIONS

As above mentioned, old antibiotics (vancomycin, daptomycin, and linezolid) have limitations because of toxicity [96,97], tolerance [103,104], drug resistance [81], and drug–drug interactions [83]. Moreover, intravenous administration requires an intravenous line, and oral administration of linezolid also presents a potential problem of compliance [111]. Thus, the use of highly efficacious and relatively easy to use antibiotics for the treatment of ABSSSI in patients with depression is of particular clinical relevance.

Dalbavancin is a new lipoglycopeptide *in vitro* active against multidrug-resistant pathogens currently approved in the USA and Europe for the treatment of ABSSSI [115,116]. In a recent survey on 1141 Methicillin Resistant Staphylococcus aureus (MRSA) isolates with minimum inhibitory concentration of vancomycin at least 2 μg/ml, dalbavancin demonstrates the highest intrinsic activity compared with daptomycin and linezolid [117]. Dalbavancin has an excellent safety profile, low drug–drug interaction and a long half-life (up to 14 days) that simplifies the ABSSSI treatment with just a single shot administration of the total dose or two administrations once weekly for two weeks [118▪]. The facilitated way of administration may improve the adherence to antibiotic therapy in depressive patients who have both difficulties in motivation and cognitive deficits. However, it should be borne in mind that the dose should be reduced among patients with severe chronic renal

disease, not undergoing hemodialysis [119], as it is the case of many elderly with depression. The two registration DISCOVER trials showed noninferiority of dalbavancin respect to vancomycin and oral linezolid (allowed as switch after at least three days of vancomycin) comparator arm for the achievement of the primary endpoint, that is, early improvement of ABSSSI within the first 48 to 72 h. In these trials, the overall incidence of adverse events was 32.8% among dalbavancin-treated patients compared with 37.9% of comparator-treated patients (*P*: 0.05); notably, the incidence of deaths was 0.8 and 2.5% (*P*: 0.02) and of diarrhea 0.2 and 1.1%, respectively (*P*: 0.03) [120]. For these reasons, dalbavancin may narrow the efficacy-effectiveness gap observed in the management of depressed patients with ABSSSI. A single dose of dalbavancin in hemodynamically stable patients with depression and ABSSSI could be considered as a safe treatment regardless of clinical suspicion of MDR gram-positive bacteria. For patients with risk factors for gram-negative infection, we also suggest adding a second drug, usually oral fluoroquinolones, ensuring, by follow-up electrocardiogram (ECG), that any antidepressant treatment is being undertaken safely.

Several studies have found a strong association between longer hospitalization, quality of life, outcome, and risk of onset or worsening of depression [121]. Therefore, an additional benefit of dalbavancin may relate to avoiding or reducing hospitalization and consequently reducing the risk of sociocultural isolation and marginalization as well, which can further worsen depression symptoms [122]. Moreover, unemployment is a well-recognized risk factors for depression, whereas fast returning to work and reintegration in the community has been shown to be protective [123]. Permitting earlier discharge and rehabilitation of social competences is now on the 'agenda of mental health professionals' [123]. A retrospective study performed in Spain and including 69 patients with different gram-positive infections (e.g., prosthetic joint infections, ABSSSI, osteomyelitis), showed that dalbavancin therapy reduced hospital stay by a mean of 16 days per patient [124]. Therefore, dalbavancin can offer a special support for management of depressed patients with infections, especially in the case of those who are more vulnerable.

CONCLUSION

In conclusion, depression is a leading cause of disability and disease burden in the developed countries. Infections are common in patients with depression and associated with poor quality of life, low adherence to appropriate medical therapy and high morbidity rates. Thus, a holistic approach should be implemented assessing patient's personal and contextual problems, the severity and peculiarities of symptoms of both conditions and his/her general physical condition. The pharmacological treatment of depression is fundamental for both conditions; nevertheless, the patient's adherence to the treatment and drug–drug interactions between antidepressants and antibiotics may play a crucial role. Regarding this aspect, future integrated approach that incorporates assessment and treatment of both depression and infections seems essential to enhance the daily life and quality of life of our patients.

Further research is needed to determine if nonpharmacological interventions or depression treatment may reduce the incidence of infection and, similarly, whether antibiotic treatment for infections might improve depression symptoms. Moreover, dual therapy trials are needed to assess if depression and infection outcomes can be improved regarding the comorbidity.

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