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Review Article

No more tears from surgical site infections in interventional pain management

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ABSTRACT

As the field of interventional pain management (IPM) grows, the risk of surgical site infections (SSIs) is increasing. SSI is defined as an infection of the incision or organ/space that occurs within one month after operation or three months after implantation. It is also common to find patients with suspected infection in an outpatient clinic. The most frequent IPM procedures are performed in the spine. Even though primary pyogenic spondylodiscitis *via* hematogenous spread is the most common type among spinal infections, secondary spinal infections from direct inoculation should be monitored after IPM procedures. Various preventive guidelines for SSI have been published. Cefazolin, followed by vancomycin, is the most commonly used surgical antibiotic prophylaxis in IPM. Diagnosis of SSI is confirmed by purulent discharge, isolation of causative organisms, pain/tenderness, swelling, redness, or heat, or diagnosis by a surgeon or attending physician. Inflammatory markers include traditional (C-reactive protein, erythrocyte sedimentation rate, and white blood cell count) and novel (procalcitonin, serum amyloid A, and presepsin) markers. Empirical antibiotic therapy is defined as the initial administration of antibiotics within at least 24 hours prior to the results of blood culture and antibiotic susceptibility testing. Definitive antibiotic therapy is initiated based on the above culture and testing. Combination antibiotic therapy for multidrug-resistant Gram-negative bacteria infections appears to be superior to monotherapy in mortality with the risk of increasing antibiotic resistance rates. The never-ending war between bacterial resistance and new antibiotics is continuing. This article reviews prevention, diagnosis, and treatment of infection in pain medicine.

Keywords: Anti-Bacterial Agents; Antibiotic Prophylaxis; Blood Culture; Cefazolin; C-Reactive Protein; Discitis; Drug Combinations; Drug Resistance, Bacterial; Guideline; Serum Amyloid A Protein; Surgical Wound Infection; Vancomycin.

INTRODUCTION

It is not rare to find infectious diseases in patients with a common pain syndrome. Cellulitis near the prosthetic leg in patients with stump pain or diabetic foot in diabetic peripheral neuropathy, pneumonia in old, debilitated, or immunocompromised cancer patients with herpes zoster, and septic arthritis or spondylodiscitis in patients with degenerative disorders are infections in common pain syndromes which should not be missed. In addition, as the field of interventional pain management (IPM) grows, the risk of surgical site infections (SSIs) is also increasing.

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SSI is a distressing outcome to both patient and physician, requiring a long unexpected hospital stay, increased morbidity, and high medical expenses. SSI is defined as an infection of the incision or organ/space that occurs within one month after operation or three months after implantation. It can be divided into superficial incisional (such as, skin and subcutaneous tissue), deep incisional (such as, fascia and muscle), or organ/space SSI. Surgical wounds are also classified into clean, clean-contaminated, contaminated, or dirty-infected [1,2].

SSI can be recognized by purulent discharge at the incisional site, isolation of organisms taken from the incisional site, opening of the wound, clinical signs of inflammation, such as dolor (pain), tumor (swelling), rubor (redness or erythema), and calor (warmth or increased heat), or evidence of infection from imaging diagnosis [3].

SSI can be reduced by following various guidelines with evidence-based preventive measures, diagnosed with a careful follow-up of wound care and through the blood culture and antibiotic susceptibility or sensitivity testing (AST) if SSI is suspected, and managed with the proper selection of an antibiotic.

The 2nd edition of the recommendations of the World Health Organization (WHO) for several controversial core topics related to SSI was published in 2018 [4].

The great evolution in the field of prevention and treatment of SSI was the discovery of antibiotics. In 1911, Arsphenamine (compound 606, Salvarsan®; Hoechst AG, Frankfurt, Germany), known as Paul Ehrlich's magic bullet which was an agent to treat syphilis caused by *Treponema pallidum*, was discovered and became known as the first modern antibiotic [5–7]. After the discovery of penicillin in 1928 by Alexander Fleming, the golden age of natural antibiotics began and continued until the antibiotic resistance crisis following the first detection of the methicillin-resistant *Staphylococcus aureus* (MRSA), which is resistant to β-lactams, in 1961 [8,9]. Antibiotic resistance, one of the medical problems facing humans, may be viewed as a defense strategy from the standpoint of the bacteria.

Antibiotics and antimicrobials are generally accepted as being effective agents against bacteria and microorganisms (viruses, fungi [yeasts or molds], protozoa, as well as bacteria), respectively. However, antibiotic also means "against life"; therefore, any drug which kills microorganisms (germs) in the human body is called an antibiotic. In this review, antibiotics will mean antibacterials, a narrowed definition.

Antibiotics can be divided into bacteri(o)cidal or bacteri(o)static agents, broad or narrow spectrum agents, or by their mode of action [10,11].

Most SSIs are treated by definitive antibiotic therapy according to AST. However, in a septic condition after IPM, empirical antibiotic therapy should start before receiving the AST results [12].

There are several approved antibiotics which combine β-lactams with β-lactamase inhibitors [13,14]. In addition, combination antibiotic therapy, compared to monotherapy, for multidrug-resistant Gram-negative bacteria (MDRGNB) infections showed reduced mortality and antibiotic resistance rates [15].

This review introduces prevention, diagnosis, and management for infection in the field of pain medicine.

MAIN BODY

1. Prevention of SSIs

1) Reviewing various recommendations related to the prevention of and a conclusive checklist for preventing SSI in IPM

(1) Recommendation for prevention of SSI by the WHO in 2018

The 2nd edition of the recommendations by the WHO for several controversial core topics related to prevention of SSI was published in 2018 [4]. They made 29 recommendations covering 23 topics.

Preoperative decolonization by intranasal application of 2% mupirocin ointment for the prevention of *S. aureus* infection in nasal carriers, preoperative surgical antibiotic prophylaxis (SAP) within two hours before incision, prohibition of preoperative hair removal, preoperative surgical hand preparation before putting on sterile gloves, and postoperative prolongation of SAP in certain cases are strongly recommended with moderate evidence.

Preoperative surgical site preparation using alcohol-based antiseptic solutions based on chlorhexidine gluconate (CHG) is also strongly recommended with moderate to low evidence.

Preoperative SAP before incision, depending on the type of surgery, is strongly recommended with low evidence.

(2) Prevention guidelines for SSI from the Centers for Disease Control and Prevention (CDC) in 2017

The United States CDC published 13 items as preven-

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tion guidelines for SSI. Recommendation categories were divided into a strong (IA: high to moderate-quality evidence; IB: low-quality evidence; IC: state or federal regulation), weak (II; any quality evidence), or no recommendation (low to very low-quality evidence) [1].

Taking a shower or bath with soap or an antiseptic agent the night before the operation is an accepted practice (IB). Intraoperative skin preparation with CHG is also helpful unless contraindicated (IA). Parenteral SAP administration is timed so that a bactericidal concentration is established in the serum and tissues when the incision is made (IB). Redosing after an operation is not needed in clean and clean-contaminated wounds, even in the presence of a drain (IA). Even in implantation procedures with clean and clean-contaminated wounds in patients receiving systemic steroids or other immunosuppressive therapy, redosing is not needed even in the presence of a drain (IA).

Neither intraoperative antibiotic irrigation of the deep or subcutaneous tissues nor soaking prosthetic devices in antibiotic solutions before implantation is recommended (no recommendation). Soaking prosthetic devices in antiseptic solution before implantation or repeated application of antiseptic agents to the skin immediately before closing the incision is not helpful (no recommendation). Do not apply antibiotic agents (such as ointments, solutions, or powders) to the incision sites (IB). In addition, application of antibiotic dressings to incision sites after primary closure in the operating room is also not recommended (no recommendation). Application of an antibiotic sealant or plastic adhesive drapes immediately after intraoperative skin preparation is also not necessary (II). Intraoperative irrigation of deep or subcutaneous tissues or intraperitoneal lavage in contaminated or dirty abdominal wounds with aqueous iodophor solution is also not necessary (II).

However, application of autologous platelet-rich plasma is not necessary (II). Blood transfusion, if needed, may be given without worry of increased rate of SSI (IB). Use of triclosan-coated sutures is also helpful (II).

The target for perioperative glucose blood level is less than 200 mg/dL, regardless of diabetes (IA). However, the issue for the optimal hemoglobin A1C is not determined (no recommendation). Maintenance of perioperative normothermia, optimizing tissue oxygen delivery, and adequate blood volume replacement are helpful for reducing SSI (IA).

(3) Recommendations for reducing SSI in spine surgery by the North American Spine Society (NASS) in 2013

Most interventional pain procedures are performed on the spine. Therefore, it is helpful to review and adapt the NASS recommendation for SAP in spine surgery [16].

A single dose of SAP in a typical uncomplicated lumbar laminotomy/discectomy, in an uninstrumented spine surgery, and even in an instrumented spine fusion, is effective for reducing SSI. Despite appropriate SAP, diabetic patients show an increased rate of SSI. However, there is insufficient evidence that obesity increases the rate of SSI. In addition, despite appropriate SAP, the rate of SSIs is 0.7%–10% regardless of comorbidities. When choosing SAP, risk factors and allergies of the patient, length and complexity of the procedure, and antibiotic resistance should be considered. Intraoperative redosing within 3–4 hours in a prolonged procedure is suggested.

Alternated SAP regimens, such as redosing, Gram-negative coverage/broad-spectrum SAP, or intra-wound vancomycin or gentamicin application, are needed in patients with comorbidities (diabetes, neuromuscular disorder, spinal cord injury, or spinal trauma) and patients undergoing complicated instrumented surgery. Prolonged SAP may be considered in complex situations, such as high glucose level (125 mg/dL preoperatively or 200 mg/dL postoperatively), trauma, spinal cord injury, neuromuscular disorder, obesity, incontinence, or multilevel surgery. This prolongation or alteration of SAP recommended by the NASS, rather than the CDC, seems to take the clinician's side for the worry about feasible and tragic infections.

However, there is insufficient evidence that SSI can be reduced by early discontinuation of SAP at 24 hours in the presence of a drain and use of a drain in a single level surgery. There is also insufficient evidence whether a high dose of SAP is required in those with high body mass index, or whether alternated SAP is prepared for comorbid patients with diabetes, smoking, malnutrition, and immune deficiency. The use of vancomycin for SAP in patients with a history of MRSA is also a controversy. An additional single dose of SAP, if intraoperative redosing is necessary, reduces the risk of adverse reactions to an antibiotic, such as flushing, rashes, colitis, and Steven–Johnson syndrome.

(4) Recommendation for reducing SSI in drug delivery and spinal cord stimulation (SCS) device implantation by the American Society of Anesthesiology (ASA) in 2004

The ASA classified strength of recommendations by the evidence as follows: IA = strong recommendation supported by well-designed experimental, clinical, or epidemiologic studies; IB = strong recommendation supported by some experimental, clinical, or epidemiologic studies or strong theoretical rationale; II = suggestion by suggestive clinical or epidemiologic studies or theoretical rationale, but not validated by controlled studies [17].

① Pre- and intra-operative strategies

Postpone elective surgery if any remote infections exist. Do not remove hair, or if needed, do so immediately before operation using electric clippers (Category IA).

Preoperative blood glucose control, cessation of smoking for 30 days before the operation, continued supply of blood products, taking a shower or bath the night before surgery, a surgical scrub for 2–5 minutes with an appropriate antiseptic and then putting on a sterile gown and gloves after drying hands with a sterile towel while keeping the hands up and away from the body, and washing the incision site before performing antiseptic skin preparation are recommended (Category IB).

Preparation the skin in concentric circles from the incision site, keeping the preoperative hospital stay short, proceeding with device implantation even in risky patients with spasticity or cancer pain, or in those with remote infections, selection of a device or model suitable for patient's size and body habitus, selection of the device pocket site while considering surgical scars, ostomies, use of belts, seat belt, or wheelchair, and preoperative marking of the device's pocket site in a patient's standing position are recommended (Category II).

Performing implant surgery in an operating room rather than a procedure room, minimizing operating room traffic during implant surgery, and using a sterile draped fluoroscope are recommended (Category II).

Intravenous SAP a few hours before surgery (Category IA) and prohibition of preoperative routine use of vancomycin are recommended (Category IB).

Use of double gloves and performing minimal-touch or no-touch surgical techniques, avoidance of placing devices directly under incision lines, and closure of the implant site incisions in anatomical layers while considering subfascial placement in underweight patients are recommended (Category II).

② Postoperative strategies

Application of occlusive, antiseptic wound dressing with a sterile technique as well as prompt and aggressive treatment of threatened incisions and external cerebrospinal fluid leaks are recommended (Category II).

Removal of contaminated section or the entire system as indicated, tapering intrathecal drug or administration of substitute medication systemically to prevent or treat intrathecal baclofen or opioid withdrawal when removing the drug delivery system due to infection, and a proper antibiotic administration as determined by wound cultures and stains are recommended (Category II). Ensuring complete and permanent eradication of the infection before reimplantation with a new device is recommended (Category II).

Identifying SSI among inpatients and outpatients using the CDC definitions, prospective recording of surgical wound classification and other factors associated with the risk of SSI, periodical calculation of risk-stratified, operation-specific SSI rates, and reporting to surgical team members are needed (Categories IB and II).

(5) Summary of recommendations for preventing SSI in IPM

A checklist for preventing SSI in IPM includes 18 "do's" (preoperative: 9; perioperative: 5; postoperative: 4) and 7 "don'ts" (preoperative: 2; perioperative: 5) strategies, based on the above 4 guidelines (**Table 1**) [1,14,16,17].

2) SAP

SAP is defined as use of preoperative antibiotics for reducing intraoperative bacterial contamination to a level (minimum inhibitory concentrations, MIC) at the incision site, resulting in reducing postoperative SSIs [18,19].

The first-line SAP agent in IPM is cefazolin. If a patient is allergic to cefazolin (β-lactams), vancomycin or clindamycin is the next choice. Cefazolin or vancomycin is given intravenously according to body weight of the patients (1 gram for 80 kg or less, 2 grams for 81–160 kg, and 3 grams for over 160 kg). A different amount of clindamycin is also given intravenously according to their weight (600 mg for 80 kg or less, 800 mg for 81–160 kg, and 1,200 mg for over 160 kg). Considering MIC, cefazolin and clindamycin should be given 30–60 minutes prior to incision. However, vancomycin should be given slowly within

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Table 1. A summarized checklist for prevention and treatment of surgical site infection in interventional pain management from various guidelines [1,4,16,17]

Preoperative strategies	
Do's	Don'ts
1. Encourage patients to stop smoking for 1 month before operation [17]. 2. Control preoperative blood glucose level less than 125 mg/dL [16]. 3. Keep the preoperative hospital stay short [17]. 4. Let patients take a shower or bath with soap or an antiseptic agent the night before operation [1,16]. 5. Perform preoperative decolonization by intranasal application of 2% mupirocin ointment for the prevention of *Staphylococcus aureus* infection in nasal carriers [4]. 6. Administer intravenous surgical antibiotic prophylaxis before surgery: 1 gram of cefazolin or 600 mg of clindamycin within 30 min and 1 gram of vancomycin within 2 hr [16]. 7. Perform a surgical scrub for 2–5 min, and then donning a sterile gown and gloves after drying hands with a sterile towel while keeping the hands up and away from the body [4]. 8. Select a suitable device and device pocket site in implantation surgery [17]. 9. Prepare the skin in concentric circles from the incision site with chlorohexidine gluconate [1,4].	1. Do not perform elective surgery if any remote infections exist [17]. 2. Do not remove the hair, or if needed, do so immediately before operation using electric clippers [4,17].
Intraoperative or perioperative strategies	
10. Perform implant surgery in an operating room rather than a procedure room, minimize operating room traffic during implant surgery, and use a sterile draped fluoroscope [17]. 11. Keep perioperative blood glucose level less than 200 mg/dL. Maintain normothermia and replace adequate blood volume to optimize tissue oxygen delivery [1]. 12. Perform blood transfusion, regardless of issue of increased surgical site infection rate [1]. 13. Apply autologous platelet-rich plasma [1]. 14. Use triclosan-coated sutures [1]. 15. Control postoperative blood glucose level less than 200 mg/dL [16]. 16. Continue surgical antibiotic prophylaxis in case of implantation after operation [4]. 17. Treat established infection including removal of contaminated or entire system as indicated and administer an appropriate antibiotic. After complete eradication of infection, reimplantation is permitted with a new device [17]. 18. Record surgical site infection and risk evaluation prospectively [17].	3. Do not perform intraoperative antibiotic irrigation of the subcutaneous or deep tissues or do not soak prosthetic devices before implantation [1]. 4. No need for intraoperative irrigation of deep or subcutaneous tissues or intraperitoneal lavage in contaminated or dirty abdominal wounds with aqueous iodophor solution [1]. 5. Do not apply antibiotic agents or antibiotic dressing to the incision [1]. 6. Do not place devices directly under incision lines [17]. 7. No need for redosing in implantation surgery with clean and clean-contaminated wounds or even in the presence of a drain in patients receiving systemic steroids or other immunosuppressive therapy [1].

Table 2. Surgical antibiotic prophylaxis for interventional pain procedures [20,21]

Antibiotics	Standard intravenous dose per body weight (kg)	Administration timing prior to incision	Redosing interval	Reason for choice
Cefazolin	1 gram ≤ 80 kg 81 kg < 2 grams ≤ 160 kg 3 grams > 160 kg	30–60 min	3–4 hr (Crcl > 50 mL/min) 8 hr (Crcl = 20–50 mL/min) 16 hr (Crcl < 20 mL/min)	First-line
Clindamycin	600 mg ≤ 80 kg 81 kg < 800 mg ≤ 160 kg 1,200 mg > 160 kg	30–60 min	6 hr regardless of renal function	Beta-lactam allergy
Vancomycin	1 gram ≤ 80 kg 81 kg < 2 grams ≤ 160 kg 3 grams > 160 kg	Within 120 min	8 hr (Crcl > 50 mL/min) 16 hr (Crcl = 20–50 mL/min) None (Crcl < 20 mL/min)	Beta-lactam allergy and known MRSA colonization
Teicoplanin	400 mg ≤ 65 kg 65 kg < 600 mg ≤ 99 kg 100 kg < 800 mg ≤ 130 kg 130 kg < 1,000 mg ≤ 166 kg 167 kg < 1,200 mg ≤ 200 kg	Within 60 min intravenous injection administered by either as a bolus over 3–5 min or as continuous infusion over 30 min	12 hr regardless of renal function	Allergy to vancomycin

Crcl: creatinine clearance, MRSA: methicillin-resistant *Staphylococcus aureus*.

120 minutes prior to incision. If the renal function (creatinine clearance) is decreased, the redosing interval should be increased. If patients have an allergy to the vancomycin, teicoplanin is an alternative antibiotic which has a long half-life, lower nephrotoxicity, and a lack of requirement for serum assays (**Table 2**) [20,21].

The consensus for both the choice of appropriate SAP for the reimplantation of a spinal cord stimulator after device removal due to infection and the sufficient duration of reimplantation after control of the infection has not been established [22,23].

2. Diagnosis of SSI

SSI is defined as an infection of the incision or organ/space that occurs within 30 days after an operation or within 90 days after implantation. SSI involves ① the skin and subcutaneous tissue of the incision (superficial incisional infection) and/or ② the deep soft tissue (fascia and muscle) of the incision (deep incisional infection) and/or ③ any part of the anatomy (organs or space infection) other than the incision that was opened or manipulated during an operation. SSI is confirmed by 1 of 4 categories: ① purulent discharge, ② isolation of causative organisms, ③ at least 1 of 4 symptoms or signs (pain/tenderness, localized swelling, redness, or heat), or ④ diagnosis by a surgeon or attending physician [2].

Three major factors that increase the risk of SSI include ① operation lasting more than the duration cut-off point hours (> 75% cut-off value in hours), ② contaminated (class 3) or dirty/infected (class 4) wound, and ③ the ASA Classification 3 (severe systemic disease), 4 (incapacitating systemic disease), or 5 (moribund patients). Therefore, the sum of the basic SSI risk index score can be counted from 0 to 3 (no, mild, moderate and high) immediately after an operation. Regarding the duration of an operation, prolonged surgeries increase the risk of SSI. The cut-off sampling method is a selecting method for "inclusion (positive) or exclusion (negative) if the sample is at/above or below a predetermined threshold. The 25%–75% cut-off value or point near the median value is generally accepted, as it is located within a normal threshold. For reference, the related cut-off value for the duration for spinal surgeries is two hours [2].

1) Inflammatory markers

The most frequently used laboratory tests for diagnosis of and follow-up for SSI are white blood cell (WBC) count, erythrocyte sedimentation rate (ESR), and C-reactive

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protein (CRP). In addition, procalcitonin, serum amyloid A (SAA), and presepsin have recently been considered as useful inflammatory markers. However, almost 25% of patients may show abnormally increased non-specific inflammatory markers of CRP and ESR [24].

There are various plasma proteins which show a change in their concentration in the acute-phase response. The acute phase reactant plasma proteins include protease inhibitors (increased concentration of α1 antitrypsin and α1 antichymotrypsin, but decreased concentration of inter-α-antitrypsin), coagulation proteins (increased concentration of fibrinogen, prothrombin, factor VIII, and plasminogen), complement proteins (increased concentration of C1s, C2, B, C3, C4, C5, and C1 inhibitor, but decreased concentration of properdin), transport proteins (increased concentration of haptoglobin, hemopexin, and ceruloplasmin), and other proteins (increased concentration of CRP, SAA, fibronectin, alpha-1 acid glycoprotein, and group-specific component or vitamin D-binding globulin, but decreased concentration of albumin, transthyretin, high density lipoprotein, and low-density lipoprotein) [25].

(1) CRP

The 'C' of CRP is a protein, originating from the reaction with the C-polysaccharide of the cell wall of *Streptococcus pneumoniae*. CRP is composed of 5 identical protomers (a pentamer), which have a recognition face with a phosphocholine binding site with Phe-66 and Glu-81 residues in a calcium-dependent manner [26]. It is secreted by the liver, corresponding to inflammatory cytokines, especially interleukin 6, after trauma, malignancy, inflammation, or infection [27].

In a retrospective spinal fusion study, the preoperative reference value was less than 0.5 mg/dL (5 mg/L). Postoperative maximal CRP value was reached on the 3rd day with 13.5 mg/dL in the non-infection group, compared to on the 2nd day with 21.5 mg/dL in the infection group. The mean CRP value in the non-infection group showed a steady decrease from the 3rd day to the 8th day, showing a statistically significant lower value from the 7th day, compared to that of the infected group. Therefore, the maximal peak on the 7th day over 22.5 mg/dL (compared to the 3rd day in the non-infection group), failure to decrease the CRP (compared to from the 3rd day in the non-infection group), and a late second peak on the 12th day (compared to the 8th day in the non-infection group) may predict SSI [28]. With a combined result with another study [24], normal postoperative peak CRP value, 13.5 mg/dL, on the 3rd day will show a first-order elimination with a half-life of 2.6 days; therefore, the CRP value will become theoretically normalized at less than 0.5 mg/dL on the 16th day after 13 days, 5 elimination half-lives.

(2) ESR

Traditionally, ESR means a falling rate (mm/h) of erythrocytes in the plasma of anticoagulated blood specimen (2 mL of venous blood with 0.5 mL of sodium citrate) in a transparent capillary tube (length 200 mm and diameter 2.55 mm) in a vertical position after 1 hour, using the Westergren method, before application of automated analyzers. The ESR is balanced and determined by the fibrinogen and zeta potential (negative charge of erythrocytes). Rouleaux formation, stacks of the erythrocytes, can occur in a high concentration of positively charged fibrinogen and immunoglobulin due to inflammation. ESR can rise in malignancy, temporal arteritis, renal disease, and collagen vascular diseases, and it can also rise with a mild degree in the aged, females, and cases of pregnancy, anemia, and other elevated fibrinogen conditions [29].

In a prospective spine surgery study, the best cut-off value for elevated ESR level for identifying SSI was over 51.5 mm/h on the 6th day postoperatively, compared to over 5.94 mg/dL and 3.49 mg/dL for CRP levels on the postoperative 3rd and 6th days, respectively. However, the data were only collected preoperatively, the 3rd day postoperatively, and the 6th day postoperatively [30]. It is clear that the ESR level is increased after an increase of an acute phase reactant protein, such as CRP.

In another prospective spine surgery study, the maximum mean peak ESR level was seen on the 4th day and normalized on the 14th the postoperatively in the non-infection group. On the same 4th day postoperatively, the instrumentation surgery showed a higher maximum mean ESR level with 102 mm/h than in non-instrumentation surgery, with 75 mm/h [31].

In conclusion, the ESR value in the non-infection group starts in the normal range at less than 10 mm/h preoperatively; it shows elevation to an abnormal level of over 10 mm/h from the 4th day. and becomes normalized over 2 weeks postoperatively. In addition, the elevated ESR may show in the aged, and those with massive intraoperative blood loss, and with prolonged duration of operation and anesthesia [32].

(3) WBC count

A preoperative normal WBC count is roughly considered

to be between 5,000 and 10,000/mm^3. It is composed of neutrophils (60%), lymphocytes (35%), monocytes (2%–8%), eosinophils (1%–4%), and basophils (0.5%–1%) [33]. The WBC can also be divided into granulocytes (neutrophils, basophils, and eosinophils) and non-granulocytes (lymphocytes and monocytes). Leukocytosis (> 10,000/mm^3) may indicate infection as well as inflammation, tissue damage, dehydration, thyroid storm, leukemia, or steroid use.

In a retrospective spine surgery study, the mean WBC count was increased on the 1st day up to 12,000/mm^3 and normalized at less than 10,000/mm^3 on the 4th–6th day postoperatively in both non-infected simple discectomy and complicated fusion surgeries [34]. In a prospective spine surgery study, the postoperative change of mean WBC count showed a very similar pattern, representing a peak up to 14,000/mm^3 on the 1st day, being maintained at the abnormal level of 11,000/mm^3 on the 3rd day, and normalized to 7,800/mm^3 on the 7th day [35].

Generally, surgical stress increases the proportion of neutrophils, but decreases the proportion of lymphocytes. Re-increase of neutrophil count after several days postoperatively may indicate an important sign of SSI due to bacteria. The differential WBC count, especially lymphopenia, may be helpful in diagnosing early stages of SSI after spinal surgery. The preoperative normal lymphocyte proportion (35%) decreases to 10% on the 1st day, rapidly increases to 20% on the 4th day, and finally recovers to the normal range on the 21st day in the non-infection group. However, in the infection-group, the lymphocyte proportion decreases to 7%–8% on the 1st day, and then it decreases slightly on the 4th day, but maintains the low proportion of less than 10% even till 7th day postoperatively. Therefore, lymphopenia of less than 10% or 1,000/mm^3 on the 4th day postoperatively indicates SSI [33].

(4) Procalcitonin

Procalcitonin, a 116-amino acid peptide, is present in an undetectable level of less than 0.04 ng/mL in a normal state; however, the elevated procalcitonin level is considered to have extra-thyroidal pathologies, including bacterial infections. As a precursor of calcitonin, it is synthesized by the parafollicular cells (C cells) of the thyroid, hepatocyte, and peripheral monocytes and is in charge of calcium homeostasis [36].

In a prospective spine surgery study, the mean postoperative procalcitonin level was continuously increased over 4 to 10 ng/mL from the 1st to 5th days in the SSI group. In the non-infection group, the procalcitonin level is slightly increased from the 1st to 3rd day, but is maintained at a similar level of less than 1 ng/mL on the 4th and 5th days. Postoperatively, procalcitonin rather than CRP showed better specificity with the same 100% sensitivity. On the contrary, WBC count and ESR showed low sensitivity/high specificity and high sensitivity/low specificity, respectively. The great merit of procalcitonin is that it is less affected by surgical trauma, unlike CRP, ESR, and WBC, but responds to endotoxin. It is also helpful to determine the prognosis and risk of sepsis. However, the demerit of procalcitonin is that measuring procalcitonin is more expensive than other inflammatory markers [36].

In a prospective acute spinal cord injury surgery, preoperative procalcitonin levels were 0.08 and 0.09 ng/mL in the infection-group and non-infection group, respectively. Postoperative procalcitonin levels were 0.81 and 0.33 ng/mL in the infection-group and non-infection group, respectively. SSI can be suspected in a procalcitonin level over 0.5 ng/mL in the 24–48 hours postoperatively [37].

Therefore, the procalcitonin level is maintained at less than 0.04 ng/mL, or may be increased to 0.1 ng/mL in trauma cases. SSI can be suspected if the value increases over 0.5 ng/mL from the 1st day postoperatively as an early indicator of SSI.

(5) SAA

SAA is a precursor protein of amyloid A which is composed of 104 amino acids. Generally, amyloid A is a known protein which is deposited in amyloidosis. The serum concentration shows a surge of increase in the response to infection, inflammation, and trauma. It is also an effective marker because of its short half-life [38–40].

In a prospective posterior lumbar interbody fusion study, SAA level in the non-infection group was at the maximum level on the 3rd day up to 20 mg/L, and was significantly decreased but higher than the reference level (median value = 3 mg/L, less than 10 mg/L) on the 13th day [38,39].

The great merit of SAA, compared to CRP, is a rapid decrease in non-infected cases, which is very helpful for the early diagnosis of SSI. SAA is not changed while the CRP is decreased or normalized even after steroid administration. It is not altered by age or gender [39,40].

(6) Presepsin

Presepsin is a differentiation marker protein which is released from activation of the monocyte, macrophage,

or some granulocytes when lipopolysaccharide from infectious agents is recognized in the human body. It is known as a soluble N-terminal fragment of the cluster of differentiation 14 subtype (sCD14-ST). It becomes the receptor part of CD14 for the lipopolysaccharide binding protein complex. The advantage of presepsin, compared with CRP and procalcitonin, is that it is less affected by trauma, burn, or surgery. However, the disadvantage of presepsin is that it is deeply correlated with serum creatinine or bilirubin concentration related to renal function [41].

The advantage is a rapid response to infection: presepsin level is elevated within 2 hours and reaches its peak concentration within 3 hours, compared to procalcitonin level reaching its peak only within 8–24 hours [42]. The reference level of presepsin is 55–184 pg/mL regardless of gender and age [43].

In a retrospective spine surgery, the mean presepsin level was 123 pg/mL preoperatively. The mean presepsin level on the 1st day postoperatively was 169 and 678 pg/mL in a non-infection and infection group, respectively. The optimal cutoff for SSI was 258 pg/mL [44]. However, it is difficult to conclude when the elevated presepsin level decreased to the normal level in this study.

In a prospective spine surgery, the median presepsin levels were 126, 171, 194, and 147 pg/mL before, immediately after, 1 day after, and 1 week after operation in a non-infection group, respectively. The cutoff value for presepsin in a non-infection group was 297 pg/mL. However, all 3 infected patients had higher presepsin levels of over 300 pg/mL. In conclusion, the presepsin level in a non-infection group rises from immediately after the operation to the 1st day after the operation and decreased to a near-normal level on the 7th day postoperatively. Therefore, SSI should be suspected when the presepsin level is over 300 pg/mL on the 7th day postoperatively [45].

Even though presepsin, interleukin-6, and CRP are currently used for the diagnosis of sepsis, the prognostic value of the presepsin level has a positive correlation with the severity of sepsis using the Acute Physiology and Chronic Health Evaluation (APACHE) II score and the Sequential Organ Failure Assessment (SOFA) score [46].

(7) Summary of inflammatory marks in a non-infection group

There are normal changes in useful perioperative inflammatory markers in a non-infection group (**Fig. 1**).

The normal preoperative CRP value (< 0.5 mg/dL) increases up to 13.5 mg/dL on the 3rd day postoperatively. It will become theoretically normalized at less than 0.5 mg/dL on the 16th day after 5 elimination half-lives (13 days) with a first-order elimination with a half-life of 2.6 days in a non-infection group after spine surgery [24,28].

The normal preoperative ESR value in the non-infection group is less than 10 mm/h and is elevated to an abnormal level from the 4th day and becomes normalized over 2 weeks postoperatively [32].

The normal preoperative WBC count is between 5,000 and 10,000/mm^3. The WBC count has a peak up to 14,000/mm^3 on the 1st day, maintains at the abnormal level of 11,000/mm^3 on the 3rd day, and is normalized on the 7th day postoperatively [35].

The normal preoperative procalcitonin level is less than 0.04 ng/mL, and is increased to 0.1 ng/mL on the 1st day postoperatively. SSI can be suspected if the value increases to over 0.5 ng/mL from the 1st day postoperatively as an early indicator of SSI [37].

SAA level reaches the maximum level up to 20 mg/L on the 3rd day, and then significantly decreases, but is still higher than the reference level (median value = 3 mg/L, less than 10 mg/L) on the 13th day [38].

The normal preoperative presepsin level is 55–184 pg/mL, and it is elevated within 2 hours and reaches the peak of less than 258 pg/mL within 3 hours. The elevated level of presepsin is normalized on the 7th day [43,44].

2) Blood culture

In the clinical field, blood culture has emerged as an important practice when SSI is suspected. Immediately after blood sampling for blood culture, empirical antibiotic therapy should start if the result of the blood culture cannot be delayed because of increasing risk of morbidity and mortality from the bloodstream infection, while permitting an increasing risk of multidrug-resistant organisms. However, the sensitivity of blood culture in a post-antibiotic administration group (19.4%) was much lower than that in the pre-antibiotic administration culture group (31.4%) [47].

Blood culture is performed by a serial process of blood sampling, culturing (to grow microorganisms in an appropriate growth medium), and identification of the causative agent. The blood is collected from the vein in a sterile manner. It is drawn into the 2 bottles which are designed for the growth of aerobic and anaerobic organisms separately. A large volume of up to 20 mL of blood for each test is needed for incensement of its sensitivity. Drawing blood two to four times may be needed. The

bottles contain an anticoagulant, such as sodium polyanethol sulfonate, that does not interfere with the growth of the bacteria. Five days of standard incubation time at body temperature in an automated system is needed for recovery of major organisms, such as *Haemophilus*, *Aggregatibacter*, *Cardiobacterium*, *Eikuenella*, *Kingella* (HACEK group) and *Brucella* species. Slow-growing organisms, such as fungi and *Mycobacterium* species, need increased incubation time. Positive bottle detection from the blood culture in an automated incubator is generated by a pH increase due to CO_2 production from microorganism growth. After Gram-staining and a sub-sample from the blood culture bottle, the pathogen identification can be obtained through ① a blood culture, directly (nucleic-acid-based methods), ② a subculture for matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) analysis and AST, and ③ bacterial purification using a bacterial pellet and enrichment [48].

3) Antibiotic resistance and AST

Antibiotic resistance is a kind of defense strategy of the bacteria's genetic ability to encode resistance genes for their survival, resulting in forging inhibitory effect of potential antibiotics [49]. The mechanisms of resistance are explained by ① restricting the access of antibiotics (GNB against carbapenems), ② making new cell processes inside the bacteria by altering the antibiotic's targets, which then creates new targets (*S. aureus* against trimethoprim), ③ changing the antibiotic's target to not fit (*Escherichia coli* against colistin or polymyxin E), ④ destroying the invading antibiotic actively using enzymes (*Klebsiella pneumoniae* against carbapenems and most of the β-lactams by making versatile hydrolytic carbapenemases) and ⑤ removing the antibiotic using pumps (*Pseudomonas aeruginosa* against fluoroquinolones, β-lactams, chloramphenicol, and trimethoprim) [50].

AST is an *in vitro* test for susceptibility of the bacteria to antibiotics. There are two methods: traditional methods and automated instrument systems. The traditional methods include broth dilution tests, the antibiotic gradient method, and disk diffusion test. The automated instrument systems include the MicroScan WalkAway System (Siemens Healthcare GmbH, Erlangen, Germany), the BD Pheonix Automated Microbiology System (BD Diagnostics, Mississauga, Canada), the Vitek 2 System (bioMerieux, Durham, NC), and the Sensititre ARIS 2X

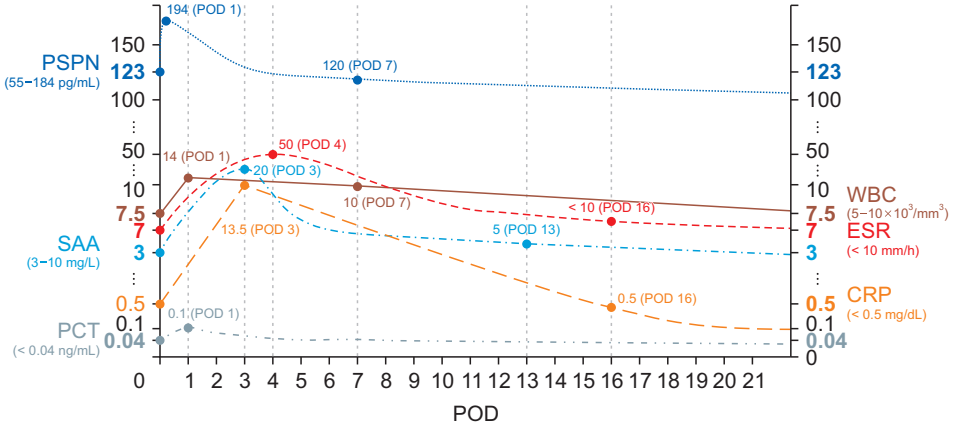

Fig. 1. The normal changes of useful perioperative inflammatory markers in a non-infection group for the detection of surgical site infection. The normal preoperative CRP value (< 0.5 mg/dL) increases up to 13.5 mg/dL on the 3rd day postoperatively. It will become theoretically normalized less than 0.5 mg/dL on the 16th day after 5 elimination half-lives (13 days) with a first-order elimination with a half-life of 2.6 days in a non-infection group after spine surgery [24,28]. The normal preoperative ESR value in the non-infection group is less than 10 mm/h and is elevated to an abnormal level from the 4th days and becomes normalized over 2 weeks postoperatively [32]. The normal preoperative WBC count is between 5,000 and 10,000/mm^3. The WBC count has a peak up to 14,000/mm^3 on the 1st day, maintains at the abnormal level of 11,000/mm^3 on the 3rd day, and is normalized on the 7th day postoperatively [35]. The normal preoperative PCT level is less than 0.04 ng/mL, is increased up to 0.1 ng/mL on the 1st day postoperatively. Surgical site infection can be suspected if the value increased over 0.5 ng/mL from 1st day postoperatively as an early indicator of SSI [37]. SAA level reaches the maximum level up to 20 mg/L on the 3rd day, and significantly decreases but higher than the reference level (median value = 3 mg/L, less than 10 mg/L) on the 13th day [38]. The normal preoperative PSPN level is 55–184 pg/mL, and it is elevated within 2 hours and reaches the peak of less than 258 pg/mL within 3 hours. The elevated level of PSPN is normalized on the 7th day [43,44]. POD: postoperative day, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, WBC: white blood cell, PCT: procalcitonin, SAA: serum amyloid A, PSPN: presepsin.

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(Trek Diagnostic Systems, Oakwood Village, OH) [51].

The Clinical and Laboratory Standards Institute (CLSI) publishes the book, *Performance Standards for Antimicrobial Susceptibility Testing* annually [52]. The European Committee on Antimicrobial Susceptibility Testing (EUCAST) of the European Society of Clinical Microbiology and Infectious Diseases publishes *Rationale for the EUCAST Clinical Breakpoints* for each antibiotic. It contains dosage of the antibiotic, MIC, and epidemiological cut-off values, MIC breakpoints prior to harmonization with CLSI, pharmacokinetics (PK), pharmacodynamics (PD), Monte Carlo simulations and pharmacokinetic/pharmacodynamic breakpoints, clinical data, and clinical breakpoints [53]. In addition, the U.S. Food and Drug Administration Center for Drug Evaluation and Research (US FDA CDER) was organized to establish breakpoints and interpretation categories [54].

The clinical categories of susceptibility, defined by EUCAST MIC breakpoints, are susceptible, intermediate (borderline), and resistant. The laboratory report of intermediate susceptibility confuses clinicians if available susceptible antibiotics are rare. First, antibiotics may show variable results related to penetration of the antibiotic into the specific target tissues, such as the urinary tract, pulmonary extracellular lining fluid, or alveolar macrophages. Second, if bacterial strains show borderline MICs, increased dosage of an antibiotic may improve treatment outcomes, however, it may also produce increased bacterial resistance, in reverse. Third, it is a wonder that the concept of "non-susceptible" is classified between intermediate and resistant [55]. On the other hand, interpretation of "susceptible-dose dependent" means that the bacteria can be treated with increased dosage of an antibiotic [56].

MIC is the lowest diluted concentration of an antibiotic with no growth of bacteria after overnight incubation. On the other hand, minimum bactericidal concentration (MBC) is the lowest concentration of an antibiotic that will prevent bacterial growth after subculture on to antibiotic-free media [57].

Clinical MIC breakpoints are a predetermined range that classifies bacteria as susceptible or not. The commonly defined MIC of antibiotics that they are effective in more than 80% of cases in patients with infection. Four important factors influencing the clinical response to an antibiotic are the maximum blood concentration (Cmax), the terminal half-life of the antibiotic ($T_{1/2}$), infection site concentration (Cm), and antibiotic characteristics (A). The Cm is determined by Cmax (Cm = 32 when Cmax > 400 μg/mL; Cm = 16 when 200 μg/mL < Cmax ≤ 400 μg/mL; Cm = 8 when 50 μg/mL < Cmax ≤ 200 μg/mL; Cm = 4 when 10 μg/mL < Cmax ≤ 50 μg/mL; Cm = 2 when 1 μg/mL < Cmax ≤ 10 μg/mL; Cm = 1 when Cmax ≤ 1 μg/mL). The time variable (t) is also determined by half-life (t = 1 when $T_{1/2}$ > 3 h; t = 0.5 when 1 h < $T_{1/2}$ ≤ 3 h; t = 0.25 when $T_{1/2}$ ≤ 1 h). The ratio of maximum target per blood concentration (Rtr) is dependent on the ratio of R (= Cm/Cmax, Rtr = 4 when R > 10; Rtr = 2 when 1.2 < R ≤ 10; Rtr = 1 when 0.12 < R ≤ 1.2; Rtr = 0.5 when 0.012 < R ≤ 0.12; Rtr = 0.25 when R ≤ 0.012). Each antibiotic (A) takes into account the constant of antibacterial efficacy (2: aminoglycosides; 1: beta-lactams, such as penicillins, cephems, monobactams, carbapenems, and new quinolones; 0.5: tetracyclines, macrolides, clindamycin, and polypeptides). The calculation formula for clinical MIC breakpoints is Cm × t × Rtr × A. Therefore, higher Cmax, longer $T_{1/2}$, higher Rtr, and aminoglycosides (rather than other antibiotics) can show higher breakpoints. Clinical MIC breakpoints become one when these conditions (Cmax ≤ 1, $T_{1/2}$ > 3 h, 0.12 < R ≤ 1.2, and antibiotics, such as beta-lactams and new quinolones) match [58].

There are several considerations in interpreting an AST report and prescribing an antibiotic. First of all, AST does not predict *in vivo* efficacy because of *in vitro* variability from pathogen tested, media used, incubation condition, and different evaluation methods of bacterial growth. Second, there is confusion between the MIC and breakpoints. The MIC is the minimum concentration of an antibiotic for inhibiting visible growth of a single isolate of a bacterium; breakpoints are discriminatory concentrations for interpretation of the AST to differentiate into susceptible, intermediate, or resistant according to 3 major organizations including the US FDA CDER, CLSI, and EUCAST. Third, it is better to start with a beta-lactam antibiotic, such as penicillins, cephalosporins, carbapenems, and monobactams, especially in severe infections. Fourth, there is no need to compare MICs between antibiotics because each antibiotic has different PK, such as serum or tissue concentration, and PD, such as concentration-dependent (aminoglycosides and fluoroquinolones) *versus* time-dependent (beta-lactams and vancomycin) bactericidal antibiotics. Bactericidal antibiotics can be divided into concentration-dependent and time-dependent killing. The concentration-dependent antibiotics show increased bactericidal effect as the peak concentration increases. These antibiotics exhibit a post-antibiotic effect, a persistent bactericidal effect after a limited antibiotic exposure, resulting from inhibiting protein or deoxyribonucleic acid (DNA) synthesis. The clinical benefit of concentration-dependent antibiotics is

a long-dosing interval. The time-dependent antibiotics have a continuous bactericidal effect as long as the serum concentration is greater than the MIC. Therefore, repeated dosing is necessary to maintain a free concentration above the MIC. Fifth, available formulae, such as intravenous administration or per os, cost, and co-morbid disorders should be considered [59].

3. Treatment of SSI and common infectious disorders in a pain clinic

IPM ranges from simple injections to pain surgery. Surgery includes excision or resection (-ectomy), ligation (-stomy), implantation, and morphological augmentation or reduction (-plasty). Generally, procedural antibiotic prophylaxis is not necessary in most IPM procedures, except intradiscal procedures after discography. SAP is required for spinal cord or peripheral nerve stimulation (PNS) (trials and permanent implantation), an indwelling epidural or intrathecal catheter with port/pump implantation, and osteoplasty.

In addition, cautions should be given regarding musculoskeletal infections, such as spinal infections and septic arthritis, in an outpatient clinic.

1) SSIs from implantations

One month after an operation or three months after implantation is a critical period for monitoring and early diagnosis of SSI if preventive measures are applied as recommended [2]. It is not rare to find patients who visit an outpatient clinic with an exposed pulse generator, lead, or extension wire of the spinal cord stimulator or an exposed pulse generator for their intrathecal pump [60,61].

(1) SCS implantation

The infection rate for SCS systems was 3.11% within 1 year after implantation in a retrospective study from the results of the United States payer database from 2009 to 2014. Most infections occurred 3 months after implantation of the generator. The risk factors were peripheral vascular disease and previous infection within 1 year before implantation of the generator in this study. On the contrary, other suspected risk factors, such as medical comorbidities (cardiac dysrhythmias or sleep apnea), revisions, and smoking did not affect the incidence of SSI [62].

Another retrospective study during 7.5 years between January 2007 and June 2014 showed 2.45% (67/2,327) of SSI within 1 year after implantation of SCS. The most common symptoms and signs were pain (75.4%), wound erythema (63.1%), wound drainage (49.2%), wound swelling (30.8%), fever (26.2%), wound dehiscence (21.5%), and nausea (4%), in order of frequency. Positive cultures were reported from the pocket (85.7%), lead anchoring site (28.6%), lead tips (11.99%), and blood (4.8%). The most common bacterium was *S. aureus* (83.3%) including 2 cases of MRSA strains, followed by *P. aeruginosa* (4.8%), *Streptococcus* species (2.4%), and *Serratia marcescens* (2.4%). There was no relation for increasing SSI with smoking, diabetes mellitus, and obesity. Treatment included antibiotics for all cases with both oral and intravenous (40.3%), oral only (28.4%), and intravenous only (26.9%) routes and explantation of the SCS system (77.6%). An epidural abscess on magnetic resonance imaging was noted in 3 cases. Application of occlusive dressing over the incision and postoperative antibiotics decreased the rate of infection [63,64].

For the treatment of the most common bacterium, methicillin-susceptible *Staphylococcus aureus* (MSSA), beta-lactams including anti-staphylococcal penicillins (nafcillin, oxacillin, cloxacillin, methicillin, dicloxacillin, and flucloxacillin) and cefazolin as a first-generation cephalosporin, are available [65]. Inoculum is a substance which is introduced into the body to create and increase resistance or immunity against a disease. The inoculum size is the required concentration of the expected bacterium for a standard test. It can be divided into low, standard, intermediate, or high concentration. The inoculum effect is a laboratory phenomenon of a significant increase in the MIC of an antibiotic when the number of inoculated agents is increased. The effect occurs with beta-lactams related with beta-lactamase producing bacteria. It also occurs in the first and second generation cephalosporins against *S. aureus* [66]. The cefazolin inoculum effect is defined as a significant increase of cefazolin MIC when the bacterial inoculum size is increased to ≥ 16 μg/mL at the high (10^7 colony forming units) inoculum, instead of the standard (10^5 colony forming units) inoculum. Cephalosporins show inoculum effects on *in vitro E. coli*, *P. aeruginosa*, *K. pneumoniae*, *Haemophilus influenzae*, and *S. aureus*. In cases where cefazolin is used as the first-line therapy, the cefazolin inoculum effect may lead to increased 30-day mortality [67].

The various mechanisms of the inoculum effect are explained as below: ① decreased antibacterial interaction with an individual bacterium in the circumstance of increased bacterial amounts within an infected site, ② biofilms to protect the bacteria themselves, ③ quorum-

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sensing pathways at a high bacterial inoculum using enzymes or efflux pumps, ④ the stationary phase of the bacteria with high inocula, resulting in increased pre-existing resistant bacteria and enhanced chance of mutation, and ⑤ antibiotic-mediated altruistic death (antibiotic-hydrolyzing enzymes released from initially dead bacteria to protect other remaining bacteria) [68,69].

Beta-lactamase-producing strains of MSSA are treated with a semi-synthetic penicillin (intravenous nafcillin and oxacillin or oral dicloxacillin) in patients with no allergy to penicillin. An alternative choice is first generation cephalosporins, such as intravenous cefazolin or oral cephalexin. Intravenous vancomycin is preferred for treating severe MRSA infections due to malabsorption of the oral formula. It is only used to treat MSSA infections in patients with an allergy to penicillin. Linezolid has a bacteriostatic activity for *S. aureus*, and is used for complicated skin and soft tissue infections and adult MRSA nosocomial pneumonia. Its main adverse reaction is bone marrow depression, resulting in thrombocytopenia in proportion to its dosage and duration. Daptomycin, a new class of lipopeptides, is effective against MSSA and MRSA. Intravenous administration is only available with a dose of 4 mg/kg over 30 minutes in 0.9% sodium chloride once daily for 1–2 weeks. In summary, cephalexin, second-generation beta-lactamase resistant penicillins, such as dicloxacillin or nafcillin, and clindamycin are effective for MSSA infections; clindamycin, trimethoprim/sulfamethoxazole, vancomycin, linezolid, and daptomycin are effective for MRSA infections (**Table 3**) [70].

(2) PNS

The SSI rate of PNS, resulting from its superficial placement, is supposed to be higher than that of the SCS system. The SSI rates of PNS and SCS systems have been revealed as 9.7% [71] and about 3% [62], respectively. The SSIs were found on the median day 50 (between 3 and 124 days). The most common bacterium was *S. aureus*. Therefore, the choice of an antibiotic is the same as in the treatment of SCS system implantation. Twenty-five percent of infected PNS systems were removed [71].

The lead design also affected the infection rate of the PNS system implantation: non-coiled leads, compared to coiled leads, showed 4 and 5 times higher SSI rates at 30 days and 60 days postoperatively, respectively, and 25 times higher per 1,000 indwelling days. Suggested mechanisms for a low infection rate in coiled PNS system implantation are fibrosis at the insertion site resulting in a better bacteriostatic seal at the skin, decreased the pistoning effect due to a solid anchor reducing lead movement, and a smaller insertion needle and leads [72].

(3) Intrathecal opioid pump

SSI of the intrathecal opioid pump originates from not only implantation surgery but also following the refilling process of the pump reservoir that may cause an additional continuous source of infection. Hematogenous spread from the distant organs is also the source of SSI. The causative agents can be confirmed on culture of the pus, blood, or cerebrospinal fluid. Pump pocket infection may lead to meningitis; isolated meningitis may occur without evidence of pocket infection. Symptoms and signs of meningitis vary according to the causative agent. There is high fever in *S. aureus* meningitis; low or no fever in *Staphylococcus capitis* meningitis [73].

In a retrospective study, 19 cases of infection developed among a total of 145 intrathecal pump implantations (13.1%). The mean time to develop meningitis was 2.2 months. MSSA was the most common bacterium in both SCS and PNS system implantation. Oral antibiotics can be used for superficial SSI; the pump should be removed and treated with intravenous antibiotics in cases of deep SSI [74].

(4) Epidural indwelling catheter with/without a subcutaneous injection port for analgesia

The predicted infection rate for indwelling epidural catheters without a subcutaneous injection port is one patient in 35 with an epidural catheter for cancer pain analgesia over 74 days may have a deep epidural infection, and one patient in 500 may die from infection-related causes. A total of 257 catheter-related infections occurred among 4,628 patients (5.6%) with epidural indwelling catheters: 211 patients with superficial infections, 57 patients with deep infections, and 11 patients with both superficial and deep infections. The incidence of deep infection was 1 per 2,391 indwelling days or 0.4 per 1,000 catheter indwelling days [75].

The most common bacterium in epidural indwelling catheter-related infections was *Staphylococcus epidermidis* (79%), followed by *E. coli* (17%), *S. aureus* (4%), and *Klebsiella* species (4%) [76].

S. epidermidis species are abundant, harmless, symbiont bacteria which maintain homeostasis and integrity on the human skin or mucosa; however, they can become an opportunistic pathogen causing virulence. They make colonization resistance through phenol-soluble modu-

Table 3. Antibiotics for the treatment of staphylococcal infections commonly occurred in spinal cord stimulation [69]

Type of infection	Antibiotic choice	Alternative antibiotic choice	Length of therapy
Simple skin infections			
MSSA	Cephalexin 500 mg QID PO	Clindamycin 300 mg PO QID or 600 mg IV TID	5–7 days
	Dicloxacillin 500 mg QID PO		
MRSA	Clindamycin 300 mg QID PO or 600 mg	-	
	Trimethoprim/sulfamethoxazole 160 mg/800 mg PO BID		
Complicated skin and soft tissue infections			
MSSA	Nafcillin 2 grams IV every 4 hr	Cefazolin 2 grams IV TID	2–4 weeks
		Clindamycin 300 mg PO QID or 600 mg IV TID	
MRSA	Vancomycin 1 gram IV BID	Linezolid 600 mg PO BID or IV BID	
		Daptomycin 300 mg intravenously QD	
Bacteremia, catheter-related infections, osteomyelitis, and pneumonia			
MSSA	Nafcillin 2 grams IV every 4 hr	Cefazolin 2 grams IV TID Vancomycin 1 gram IV BID	Bacteremia (2–4 weeks) catheter-related infections (2–4 weeks) without infective endocarditis osteomyelitis (2 weeks) pneumonia (10–14 days)
MRSA	Vancomycin 1 gram IV BID	Linezolid 600 mg PO BID or IV BID	
		Daptomycin 300 mg intravenously QD	

MSSA: methicillin-susceptible *Staphylococcus aureus*, MRSA: methicillin-resistant *Staphylococcus aureus*, QID: quarter in die, TID: ter in die, BID: bis in die, QD: quaque die, PO: per os, IV: intravenously.

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lin (γ or δ), quorum-sensing crosstalk, and lantibiotics. They also maintain barrier integrity-related immune cell priming and wound healing. However, when the barrier is disrupted, bacterial dysbiosis and barrier exacerbation related to extracellular cysteine protease A can occur [77,78]. It is a coagulase-negative, Gram-positive coccus, forming clusters. If the species invades the human body via prosthetic devices, some of them travel into the bloodstream (bacteremia). They also produce biofilms for protecting against antibiotics or host immunity using protective exopolymers (poly-y-glutamic acid). Other endotoxins induce phenol-soluble modulin peptide toxins that encode a methicillin-resistant island [79].

More than 80% of the coagulase-negative *Staphylococci* are resistant to methicillin. The causative agent should be collected from the peripheral blood and catheter site before empirical antibiotic therapy. Therefore, empirical antibiotic therapy starts from intravenous vancomycin in an assumed methicillin-resistant *S. epidermidis* infection. If the pathogen is methicillin-susceptible, beta-lactams, such as nafcillin and oxacillin, are the choice. Removal of the epidural indwelling catheter becomes a common practice to control the source of infection. The mortality rate from sepsis and septic shock is up to 20%–30% [80].

A retrospective study comparing the infection rate of the epidural indwelling catheter with or without a subcutaneous injection port for the treatment of cancer pain showed the same overall rate, 13.6%, in both groups. However, the infection rate per 1,000 catheter-days was lower in the port group (2.86) than in the no port group (5.97). There was no infection till 70 days in both groups [81]. Therefore, it is better to implant a subcutaneous injection port for long-duration epidural analgesia while reducing the risk of infection.

(5) Central venous port systems

Central venous port systems are also used for cancer pain control of the head, face, and neck. Available medications include opioids, non-steroidal antiinflammatory drugs, nefopam, ketamine, dexmedetomidine, steroids, and antianxiety drugs [82,83].

The most common complication after implantation of central venous port systems are infections. Infections include catheter–related bloodstream infections and pocket and/or tunnel cellulitis. A retrospective study of central venous port systems infection showed 45/1,747 (2.58%) were explanted to treat suspected infection. The calculated catheter-related infection rate was 0.067/1,000 catheter-days. The causative bacteria from the blood or catheter tip were *Staphylococcus* species, *Candida* species, and non-tuberculosis *Mycobacterium* in order of frequency [82]. The choice of an antibiotic is exactly the same as in the treatment of the epidural indwelling catheter with a subcutaneous injection port [76,80].

2) SSI from augmentation osteoplasty

A retrospective study showed that the infection rate after vertebral augmentation (vertebroplasty or kyphoplasty) with polymethylmethacrylate was very rare (0.36% [3/826]). Treatments include proper antibiotic medication through the immediate culture and biopsy/surgical procedures, including debridement of infected tissue (corpectomy) and bone cement followed by anterior column reconstruction or percutaneous pedicle screw fixation [84].

Another retrospective study showed 9 infected cases among 1,307 vertebroplasties or kyphoplasties with polymethylmethacrylate (0.69%). The most common sign and symptom was paraparesis (4 cases), followed by radiculopathy (1 case). Infection was noted within 1 month in 3 cases, and over 1 month in 6 cases. The interval between osteoplasty and surgical treatment ranged from 10 to 395 days with a mean of 118.4 days. The most common causative bacterium was *S. aureus* (3), followed by *S. epidermidis* (1), *Streptococcus agalactiae* (1), *Enterococcus faecalis* (1), and unidentified cases (3) [85].

Antibiotic (-loaded) bone cement contains an antibiotic, such as gentamicin, cefuroxime, or tobramycin [86]. Antibiotic-loaded bone cement shows a high initial peak elution of the antibiotic from the cement matrix, and then presents a gradual release over the following days. It reaches far higher antibiotic concentration than systemic administered antibiotic. However, its limitation is increasing numbers of the extended-spectrum beta-lactamases (ESBLs) producing bacteria [87].

Percutaneous osteoplasties of the various bones are extended techniques from percutaneous vertebroplasty of the vertebral body. The risk of infection from osteoplasties, rather than vertebroplasty, may be increased due to multiple bony metastases (not only in the vertebrae but also in the ribs, scapulae, sternum, humeral or femoral heads, and pelvic bones) in late stage of debilitated cancer patients [88].

3) Infections after injections

(1) Septic (or infectious) arthritis

Septic arthritis in adults is a painful infection in the joint. It is very rare (2–29/100,000 people/year) in the native (non-prosthetic) joint, but may develop into a potentially fatal emergency (3%–25% mortality) and severe morbidity with subchondral bone loss and permanent joint dysfunction if not treated within 1–2 days [89–92]. The most commonly affected joint is the knee (about 50%), followed by the hip, shoulder, and ankle, usually involving one large joint [92].

Similar to other infections, symptoms such as acute joint swelling, pain, erythema, and immobility should be considered possible evidence of septic arthritis. Risk factors for septic arthritis include ① hematogenous spread in patients with immunosuppression, rheumatoid arthritis, diabetes mellitus, old age, human immunodeficiency virus infection, a prosthetic joint, or gonorrhea, ② direct inoculation from a joint injection, surgery, or prosthetic joint, and ③ contiguous spread from a skin infection or ulcer [91].

Risk factors include being over 80 years old, rheumatoid arthritis, diabetes mellitus, joint surgery within 3 months, hip, knee, or shoulder prosthesis, skin infection with/without prosthesis, human immunodeficiency virus infection, joint pain, new joint swelling, joint stiffness, fever, and diaphoresis. Physical examination reveals limitation of motion, pain with motion and axial loading, tenderness to palpation, swelling, joint effusion, redness, heating, and fever [92].

① Septic arthritis of the knee

A diagnostic approach to septic arthritis of the knee includes history, physical examination, inflammatory markers from blood and joint aspiration (especially, synovial lactate > 10 mmol/L and interleukin-6 < 7,000 ng/mL), blood culture, and Gram-staining. Arthrocentesis is essential to identify a causative infective agent. The color (clear, straw, yellow, or yellow-green), transparency (transparent, cloudy, or cloudy-opaque) and viscosity (thick and thin, or high and low) of synovial fluid should be checked from the bedside observation, before sending the specimen to the laboratory. Non-gonococcal septic arthritis exhibits a yellow-green color, opaque transparency, and high viscosity. Laboratory findings of synovial fluid analysis include the WBC count > 50,000/mm^3 (> 10,000/mm^3 is more confirmatory), polymorphonuclear cell > 75%, positive Gram-stain (60%–80%), positive culture (> 90%), no crystallization, as well as lactate > 10 mmol/L and interleukin-6 < 7,000 ng/mL. On the contrary, normal synovial fluid analysis shows clear colored, transparent, and high/thick viscosity from the bedside observation, and laboratory reports include a WBC count < 200/mm^3, polymorphonuclear cell < 25%, negative Gram-stain, negative culture, negative polymerase chain reaction, and no crystallization [91].

Causative bacteria (over 70% of all causative agents) in adult septic arthritis are *Staphylococci* (56%: MSSA [42%], MRSA [over 10%], and coagulase-negative *Staphylococci* [3%]), *Streptococcus* species (16%: *Streptococcus viridans* [1%], *S. pneumoniae* [1%], and other *Streptococci* [14%]), Gram-negative cocci (*Neisseria gonorrhoeae* [1%–2%] and *Neisseria meningitidis*), and Gram-negative bacilli (15%: *P. aeruginosa* [6%], *E. coli* [3%],*Proteus mirabilis* [1%],*Klebsiella* [1%],and *Enterobacter*), in order of frequency [91,92].

If septic arthritis of the knee is suspected from the history and physical examination, laboratory examination from the blood and synovial fluid with imaging studies including radiography and magnetic resonance imaging are needed. If the lactate is more than 10 mmol/L and interleukin-6 is less than 7,000 ng/mL from synovial fluid analysis, empirical antibiotic therapy can be started according to the result of Gram-positive staining of the causative agent. If the result is Gram-negative staining and a synovial WBC count > 50,000/mm^3, initiating an empirical broad-spectrum antibiotic therapy is also recommended. Arthroscopic debridement or open arthrotomy (or serial closed-needle aspirations) should be performed immediately after empirical antibiotic therapy. According to the result of blood culture, definitive antibiotic therapy should be started and follow-up laboratory examinations should also be traced [93].

Definitive antibiotic therapy includes ① 1 gram of vancomycin or 600 mg of linezolid every 12 hours for the treatment of MRSA and coagulase-negative *Staphylococcus* species, ② 2 grams of nafcillin every 6 hours or 900 mg of clindamycin every 8 hours for the treatment of MSSA, ③ 2 million units of penicillin G every 4 hours or 2 grams of ampicillin every 6 hours for the treatment of group A *Streptococci* (*Streptococcus pyogenes*) and group B *Streptococcus* (*Streptococci agalactiae*), ④ 2 grams of ampicillin every 6 hours or 1 gram of vancomycin every 12 hours for the treatment of *Enterococcus* species, ⑤ 3 grams of ampicillin-sulbactam every 6 hours for the treatment of *E. coli*, and ⑥ 2 grams of ampicillin every 6 hours or 500 mg of levofloxacin daily for the treat-

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ment of *P. mirabilis* [93].

Gächter classification of the arthroscopic view in septic knee arthritis is divided into 4 stages. Stage 1 exhibits opacity of the synovial fluid and redness of the synovial membrane. Stage 2 presents severe inflammation, fibrinous deposition, and pus. Stage 3 includes thickness of the synovial membrane and compartment formation. Stage 4 shows aggressive pannus with infiltration of the cartilage, followed by undermining the cartilage. Radiographic findings, such as subchondral osteolysis, osseous erosion, or cysts, show in only stage 4 [94].

② Septic arthritis of the hip

Septic arthritis of the hip can be divided into active or quiescent infections. Despite 30% (16.7%–78.4%) of negative cultures being inaccessible, *S. aureus*, including MSSA, MRSA, and methicillin-resistant *S. epidermidis*, is the most common causative bacterium. The rate of hematogenous infections ranged from 9.1% to 65.3%. *Mycobacterium tuberculosis* is commonly found in the hematogenous infection. Treatments include arthroscopic debridement/lavage and one-stage or two-stage total hip arthroplasties, as well as a definitive antibiotic therapy [95].

③ Septic arthritis of the shoulder

Septic arthritis of the shoulder has a lower incidence compared to that of the hip or knee in the lower extremities, ranging from 5% to 12% of all the septic arthritis. It is common in patients with hypertension, diabetes mellitus, chronic anemia, rheumatoid arthritis, and chronic pulmonary disorders. It shows poor prognosis with local complications such as recurrent effusion, drainage, subluxation, dislocation, or osteomyelitis and systemic morbidity such as septicemia, septic shock, myocardial infarction, urinary tract infection, pneumonia, or deep vein thrombosis. The most common causative bacterium is MSSA (39%), MRSA (21%), *Streptococcus* species (11%), and GNB (7%), in order of frequency. Treatment includes arthroscopic irrigation and debridement rather than arthrocentesis and definitive antibiotic therapy [96].

④ Septic arthritis of the ankle

Even though septic arthritis of the ankle makes up a small portion (7% to 15%) of all septic arthritis, it may lead to devastating morbidity (including permanent cartilage erosion, painful synovitis, and osteomyelitis) and mortality (11.5%). Risk factors include trauma, ankle joint surgery, rheumatoid arthritis, osteoarthritis, and crystalloid arthropathy. A synovial WBC count > 50,000/mm^3 and blood culture are helpful in making a diagnosis. Treatment includes open surgical drainage, arthroscopic drainage, serial aspiration, as well as empirical antibiotic therapy followed by definitive antibiotic therapy [97].

(2) Spinal infections

Spinal infection is a red-flag sign that needs an immediate antibiotic treatment after accurate confirmation of a causative agent. A significant delay of 2–6 months usually occurs before the diagnosis and treatment of spinal infection due to non-specific signs and symptoms, such as back pain (85%), fever (48%), and paresis (32%) [98]. Spinal infections account for 2%–7% of all cases of musculoskeletal infections. Incidence of spinal infections varies 1–4/100,000 population and its mortality rate ranges from 2% to 4%. An increased number of incidences in recent years have occurred due to an increased susceptible population with previous spine surgery and an improved diagnostic accuracy. Post-procedural discitis represents up to 30% of all cases of pyogenic discitis, nowadays [99]. Spinal infection is 2–5 times more frequent in the male gender [98].

The three common routes of spondylodiscitis are hematogenous spread, direct external inoculation, or spread from neighboring (contiguous) tissues. Hematogenous pyogenic spondylodiscitis affects the lumbar (60%), thoracic (30%), and cervical (10%) spine, in decreasing order of frequency. On the other hand, tuberculous spondylitis commonly affects the thoracic spine, which involves more than 2 levels, sometimes non-contiguously. Direct inoculation is of the most concern after iatrogenic IPM procedures, usually involving the posterior column of the spine [11,100]. There are 4 different spinal infections according to the involved anatomic location: ① spondylodiscitis, ② psoas abscess, ③ epidural abscess, and ④ facet joint abscess (septic fact joint). All spinal infections include spondylodiscitis with/without psoas, epidural, facet joint abscess, in order of frequency [101].

The most common causative bacterium is *S. aureus* (30%–80%), followed by GNB, such as *E. coli* (up to 25%), *Streptococcus*, and *Enterococcus* species. *M. tuberculosis* is common (up to 60%) in human immunodeficiency virus infection, and anaerobic agents cause infections in penetrating spinal trauma. However, in 1/3 of spinal infections, the causative agents cannot be identified [99].

Spinal infections can be divided into pyogenic, granu-

lomatous, or parasitic infection. A pyogenic spinal reaction is caused by most bacteria; a granulomatous spinal reaction is induced by *Mycobacterium*, fungi, *Brucella*, and syphilis. Pyogenic spinal infections are frequent in the lumbar spine, followed by the thoracic and cervical spine; tuberculosis spinal infections are common in the thoracic spine, followed by the lumbar and cervical spine. The hematogenous arterial route to the metaphyseal region is predominant in pyogenic spinal infections; Batson's paravertebral venous plexus route to the anteroinferior vertebral body is a common initiating part in tuberculosis spinal infection, resulting in spreading to the anteroinferior part of adjacent vertebral body beneath the anterior longitudinal ligament (subligamentous spread) and periosteum. Intervertebral disc involvement is common in pyogenic spinal infection; it is rare in tuberculosis spinal infection. Pyogenic spinal infections, compared with tuberculosis spinal infections, show a relatively higher fever, a shorter symptom to diagnosis interval, increased ESR and CRP, and an increased incidence in the older aged. Magnetic resonance imaging in pyogenic spinal infections shows thick and irregular abscess walls, involvement less than 3 vertebral bodies, abscess formation in the intervertebral disc, homogenous vertebral body enhancement, lumbar spine involvement rather than thoracic spine, and mild vertebral body destruction [102]. Typical magnetic resonance imaging with contrast medium administration includes ① hypointense vertebral body and disc with loss of endplate definition in T1-weighted images, ② hyperintense vertebral body and disc with loss of endplate definition in T2-weighted images or short tau inversion recovery sequence images, and ③ contrast enhancement of the vertebral body and disc (**Table 4**) [11,102].

Treatment includes medical and surgical therapies. Antibiotic therapy for the treatment of pyogenic spinal infections initiates parenterally, and parenteral administration is maintained for 6 weeks, and is converted to oral medication till symptom resolution and the normalization of inflammatory markers. The representative medical treatment for tuberculous spinal infection includes a 6-month 3-drugs regimen, using isoniazid, rifampin, and pyrazinamide, or a 4-drugs regimen with additional ethambutol [11,102]. In case of negative culture, a dual-agent empirical antibiotic therapy includes a third-generation cephalosporin (cefepime) for the treatment of GNB plus flu(clo)xacillin, clindamycin, vancomycin, or teicoplanin for the treatment of *Staphylococcus* (MSSA or MRSA) or *Streptococcus* species [11].

Surgical treatment is required for the identification of the causative agent in cases of no response to the empirical antibiotic therapy and presence of deformity or paralysis. Instead of open surgical treatment, endoscopic biopsy, debridement, and drainage is available in debilitated patients under monitored anesthetic care [101]. Treatment options of spondylodiscitis include ① minimally invasive endoscopic debridement, ② percutaneous instrumentation without debridement, ③ decompression, debridement, and instrumentation, ④ discectomy, corpectomy, and instrumentation, and ⑤ complex anteroposterior reconstruction and instrumentation.

4) Cellulitis

Cellulitis is a spreading acute infection of the deep dermis and subcutaneous tissues, presenting with redness, warmth, tenderness/pain, and swelling. More than 650,000 persons per year are admitted in hospital in the United States; 14,500,000 cases of patients visit an outpatient clinic. Tenderness, rather than itching, is more frequent in cellulitis; itching, rather than tenderness, is more common in allergic reactions and contact dermatitis [103].

The causative agent is found in only 10%–15% of cellulitis cases [103,104]. The most common causative bacterium is *beta-hemolytic Streptococcus* and *S. aureus*.

Table 4. Comparison between pyogenic and tuberculous spinal infections [11,102]

Comparison	Pyogenic	Tuberculous
Symptoms to diagnosis interval	Shorter	Longer
Fever	Higher	lower
Increased ESR and CRP	More frequent	Less frequent
Involvement of the spine	Lumbar > thoracic or cervical spine	Thoracic > lumbar or cervical
Abscess walls	Thick and irregular	Thin and smooth
Location of abscess	Intervertebral disc	Vertebral body
Vertebral body involvement	< 3 levels	Multiple levels

ESR: erythrocyte sedimentation rate, CRP: C-reactive protein.

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Group A streptococcal infection is an important cause of culture-negative cellulitis and is associated with necrotizing fasciitis; purulent skin infection is deeply associated with *S. aureus*. Mixed infection with Gram-negative and anaerobic organisms can occur in immunosuppressed and aged patients [104].

A portal of entry, such as ulcers, trauma, eczema, or cutaneous mycosis, may be revealed through careful physical examination. In severe cellulitis, skin breaks, bullae, and necrotic tissues may be found. Risk factors of lower limb cellulitis include skin breaks, lymphedema, venous insufficiency, tinea pedis, and obesity. The severity of cellulitis can be divided into 4 grades by Eron classification recommended by the Clinical Resource Efficiency Support Team (CREST) or modified Dundee classification. The standardized early warning score (SEWS), including respiratory rate, temperature, blood pressure, heart rate, and response to stimuli, allows physicians to quickly recognize a general condition in a patient with cellulitis (**Table 5**) [104].

Treatment is divided into Streptococcus/MSSA coverage and MRSA coverage antibiotics. Streptococcus/MSSA coverage antibiotics include oral antibiotics, such as ampicillin-clavulanate, cephalexin, dicloxacillin, and penicillin VK, and intravenous antibiotics, such as cefazolin (1st generation cephalosporin), ceftaroline (5th generation cephalosporin), ceftriaxone (3rd generation cephalosporin), imipenem, meropenem, nafcillin, oxacillin, penicillin G, and piperacillin-tazobactam. MRSA coverage antibiotics include oral antibiotics, such as clindamycin, doxycycline or minocycline, linezolid, and trimethoprim-sulfamethoxazole, and intravenous antibiotics, such as clindamycin, daptomycin, linezolid, telavancin, tigecycline, and vancomycin (**Table 6**) [105].

However, MRSA coverage oral antibiotics can be divided into preferred and alternative antibiotics. The preferred oral antibiotics for the treatment of soft tissue infections due to MRSA are trimethoprim-sulfamethoxazole, clindamycin, doxycycline, and minocycline. Use of alternative oral antibiotics is limited by cost, lack of clinical experience, and adverse reactions. These are linezolid, tedizolid, delafloxacin, and omadacycline [106] (**Table 7**).

Table 5. Classification for severity of cellulitis and SEWS [104]

Classification	Eron classification recommended by CREST				Modified Dundee classification			
Class I	No or well-controlled comorbidities and systemically well				No sepsis, no comorbidity, and SEWS < 4			
Class II	Systemically unwell with no uncontrolled comorbidities or systemically well with poorly controlled comorbidities				One or more significant comorbidities, no sepsis, SEWS < 4			
Class III	Marked inflammatory response or very poorly controlled comorbidities				Sepsis but SEWS < 4			
Class IV	Septic shock or life threatening necrotizing fasciitis				Sepsis and SEWS ≥ 4			
SEWS	3	2	1	0	1	2		3
Respiratory rate (breaths/minute)	≥ 36	31–35	21–30	9–20	-	-		≤ 8
SpO_2 (%)	< 85	85–89	90–92	≥ 93	-	-		-
Temperature (°C)	-	≥ 39	38–38.9	36–37.9	35–35.9	34–34.9		≤ 33.9
Blood pressure (mmHg)	-	≥ 200	-	100–199	80–99	70–79		≤ 69
Heart rate (beats/minute)	≥ 130	110–129	100–109	50–99	40–49	30–39		≤ 29
Response to stimuli	-	-	-	Alert	Verbal	Pain		None

Sepsis is defined as the presence of infection with ≥ 2 among 4 (white blood cell count < 4,000 or 12,000/mm^3, body temperature < 36°C or > 38°C, heart rate > 90 beats/minute, and respiratory rate > 20 breaths/minute).
Oral antibiotic therapy is adequate for the class I and II; Intravenous antibiotic therapy is suitable for class III and IV.
CREST: Clinical Resource Efficiency Support Team, SEWS: standardized early warning score, SpO_2: oxygen saturation by pulse oximetry.

Table 6. Antibiotic treatment of cellulitis [105]

Antibiotics	Dosage	Duration	Group
Preferred first line choice			
Flucloxacillin (Floxacillin)	500 mg every 6 hr (P.O., or IM, IV)	1–2 weeks	Penicillin
Alternative first line choice			
Cephalexin	500 mg every 12 hr (P.O.)	1–2 weeks	1st generation cephalosporin
Penicillin allery			
Clindamycin	450 mg every 12 hr (P.O.)	1–2 weeks	Lincosamide
Clarithromycin	500 mg every 12 hr (P.O.)	1–2 weeks	Macrolide
Facial cellulitis			
Co-amoxiclav or amox-clav (amoxicillin + clavulanic acid, Augmentin®)	625 mg every 8 hr (P.O.)	1–2 weeks	Penicillin with betalactamase inhibitor

P.O.: per os, IM: intramuscular injection, IV: intravenous injection.

Table 7. Oral antibiotics for the treatment of soft tissue infections due to methicillin-resistant *Staphylococcus aureus* [106]

Antibiotics	Dosage
Preferred agents	
Trimethoprim-sulfamethoxazole	1 or 2 double strength tablets every 12 hr
Clindamycin	450 mg every 8 hr
Doxycycline	100 mg every 12 hr
Minocycline	200 mg once, then 100 mg every 12 hr
Alternative agents	
Linezolid	600 mg every 12 hr
Tedizolid	200 mg every 24 hr
Delafloxacin	450 mg every 24 hr
Omadacycline	300 mg every 24 hr

Trimethoprim-sulfamethoxazole = 80 mg: 400 mg (double strength = 160 mg: 800 mg).

4. Selection of antibiotics

1) From empirical to definitive (directed or adjusted) antibiotic therapy

(1) Empirical antibiotic therapy

Empirical antibiotic therapy is defined as the initial administration of antibiotics (practical experience), which responds to potential pathogens at the suspected anatomic site of infection within at least 24 hours prior to the receipt of blood culture and antibiotic susceptibility test results (scientific proof). The door-to-needle times vary from immediately after the diagnosis of community-acquired pneumonia and infective endocarditis, to within one hour for severe sepsis and septic shock, to within six hours for acute bacterial meningitis [107–110].

Early administration of broad-spectrum antibiotics can reduce the risk of progression from severe sepsis to septic shock, by an 8% increase for each hour before initiation of antibiotics [12]. The most frequently selected empirical antibiotic in patients with severe sepsis or septic shock in an intensive care unit was carbapenems, followed by cephalosporins and penicillins. Appropriate antibiotic administration reduced mortality rates (17.5%), compared to inappropriate cases (36.8%) [111].

The check-list for empirical antibiotic therapy includes a potential bacterium for the infection site, community-*versus* hospital-acquired infection, immune state, recent antibiotic treatment during hospitalization, chronic un-

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Table 8. Empirical antibiotic therapy [113,114]

Classification of infections		First choice	Second choice or an additional antibiotic	Third choice or special cases	Beginning of empirical antibiotic	Duration for use of antibiotic or consultation	Common cases in a pain clinic
Community-acquired pneumonia	CURB 65 score ≤ 2 without sepsis	Oral ampicillin 500 mg every 8 hr	Oral doxycycline 200 mg as a one-off single dose and then 100 mg daily	Oral clarithromycin 500 mg every 12 hr	Immediately	5 days	Herpes zoster in the elderly
	CURB 65 score ≥ 3 with sepsis	Oral/IV clarithromycin 500 mg every 12 hr	Plus either IV ampicillin 1 gram every 8 hr or IV Co-amoxiclav 1.2 gram every 8 hr	Oral/IV levofloxacin 500 mg every 12 hr, if there penicillin/beta-lactam allergy or Legionella infection is suspected		5 days (10–14 days for Legionella infection)	
Unknown origin sepsis		IV amoxicillin 1 gram every 8 hr (+ IV gentamicin 80 mg every 8 hr)	IV flucloxacillin 2 grams every 6 hr if MSSA is suspected	IV vancomycin 1–2 gram every 12 hr if MRSA or penicillin/beta-lactam allergy is suspected Or additional IV clindamycin 600 mg every 6 hr if severe sepsis exists	Within 1 hr in cases of severe sepsis or septic shock	Review the response within 3 days (maximal 4 days for IV gentamicin)	All unknown origin sepsis
Infective endocarditis	Native heart valve	IV amoxicillin 2 grams every 4 hr	Plus IV flucloxacillin 2 grams every 6 hr (+ IV gentamicin 80 mg every 8 hr)	Vancomycin 1 gram every 12 hr (+ IV gentamicin 80 mg every 8 hr) when MRSA infections are suspected	Immediately	Consult to an infection specialist within 3 days	
	Prosthetic valve	Vancomycin 1 gram every 12 hr (+ IV gentamicin 80 mg every 8 hr)					
Bacterial meningitis		IV ceftriaxone 2 grams every 12 hr + IV amoxicillin 2 grams every 4 hr	Chloramphenicol 25 mg/kg (maximum 2 grams) every 6 hr if penicillin/beta-lactam allergy exists		Within 6 hr	Consult to an infection specialist or neurologist within 3 days	Patients with spinal cord stimulation or intrathecal pump implantation

Table 8. Continued

Classification of infections		First choice	Second choice or an additional antibiotic	Third choice or special cases	Beginning of empirical antibiotic	Duration for use of antibiotic or consultation	Common cases in a pain clinic
Septic arthritis	Native joint	IV flucloxacillin 2 grams every 6 hr	IV vancomycin 1 gram every 12 hr if MRSA infection is suspected		Within 24 hr	Consult to an infection specialist within 3 days	Degenerative arthritis
	Prosthetic joint	IV vancomycin 1 gram every 12 hr					Previous prosthetic joint surgery
Diabetic foot infection or osteomyelitis		IV flucloxacillin 2 grams every 6 hr + oral metronidazole 500 mg every 8 hr	IV vancomycin 1 gram every 12 hr and oral metronidazole 500 mg every 8 hr if MRSA infection is suspected		Within 24 hr	Consult to an infection specialist within 3 days	Diabetic peripheral polyneuropathy
Catheter-related urinary tract infections	Symptomatic bacteriuria with/ without sepsis	Single dose of IV gentamicin 80 mg	Single dose of oral ciprofloxacin 500 mg		Within 24 hr	7 days	Spinal cord injury or cauda equina syndrome
Skin and soft tissue infections	Mild cellulitis	Oral flucloxacillin 1 gram every 6 hr	Oral co-trimoxazole 960 mg every 12 hr or oral doxycycline 100 mg every 12 hr		Within 24 hr	5 days	Amputated patients who have stump or phantom pain and use a prosthetic leg
	Moderate or severe cellulitis	IV flucloxacillin 2 gram every 6 hr	IV vancomycin 1 gram every 12 hr if MRSA infection is suspected	Additional IV clindamycin 600 mg every 6 hr if the infection rapidly progresses		7–10 days	
	Suspected necrotizing fasciitis	Urgent debridement and IV flucloxacillin 2 gram every 6 hr	Additional IV benzyl-penicillin 2.4 grams every 6 hr Or metronidazole 500 mg every 8 hr Or IV clindamycin 1.2 grams every 6 hr	IV vancomycin 1 gram every 12 hr if MRSA infection is suspected		10 days	

CURB 65: each 5 items are given 1 point if there is new-onset confusion, urea > 19 mg/dL (> 7 mmol/L), respiratory rate ≥ 30 breaths/minute, systolic blood pressure < 90 mmHg or diastolic blood pressure ≤ 60 mmHg, and age ≥ 65, IV: intravenous, MSSA: methicillin-susceptible *Staphylococcus aureus*, MRSA: methicillin-resistant *Staphylococcus aureus*.

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derlying disorders, history of travel, resistant bacteria, and severity of infection, as well as initiation, maintenance, and interval of the antibiotic [112].

A summarized poster which has common empirical antibiotic regimens in adults according to the infection-suspected organ or system is published by the 2 separate organizations, the NHS Greater Glasgow and Clyde and NHS Grampian in 2021 and 2018, respectively (**Table 8**) [113,114]. Unlike European countries, where flucloxacillin is often used, cephalexin is commonly used in United States and Korea.

When only the report of Gram-staining (color: positive or negative) and morphology (cocci or bacilli) for the causative bacterium can obtained from the laboratory, representative bacteria can be presumed. Gram-staining, named after Hans Christian Gram in 1882, differentiates bacteria largely into 2 groups. Gram-positive bacteria have abundant (50%–95%) peptidoglycan contents in their cell wall, remaining purple after a 4-step application of the primary dye (crystal violet), trapping the agent or mordant (fixing the dye using iodine), decolorizer (ethanol/acetone), and counter staining (safranin/carbon fuchsine). However, GNB have scant (5%–10%) peptidoglycan in their cell wall, becoming pink after these 4 steps. Therefore, Gram-stainability represents a function of the cell wall. Antibiotics which inhibit cell wall synthesis of the bacteria are effective for Gram-positive bacteria (**Table 9**) [115–118].

(2) Antibiotic de-escalation

Between empirical and definitive antibiotic therapy, for the prevention of antibiotic resistance, antibiotic de-escalation refers to a strategy of discontinuing one or more components of combination empirical antibiotic therapy or decreasing the spectrum of empirical antibiotic regimen from a broad-spectrum to a narrow-spectrum antibiotic. However, unwanted adverse effects of the de-escalation include prolongation of antibiotic therapy and an inappropriate justification for unrestricted broadness of empirical antibiotic therapy. There are controversies regarding the benefits for prevention of antibiotic resistance and inappropriate prolongation of the use of antibiotics [119,120].

(3) Definitive antibiotic therapy

Definitive antibiotic therapy is based on the identification of the causative bacterium in the culture, followed by AST. The AST measures the ability of the bacterium to grow in the presence of a specific antibiotic *in vitro*. It is reported in the form of the MIC, which is the lowest concentration of an antibiotic that inhibits visible bacterial growth. It is interpreted as susceptible, (susceptible-dose dependent), intermediate, or resistant. Commonly used AST methods include broth dilution tests, the antibiotic gradient method, disk diffusion test, and automated instrument systems [51,112].

Caution should be given in interpretation of the AST results and the choice of an antibiotic. First, the AST results cannot differentiate between infection, colonization, or contamination. There is no need to treat for the latter two. Second, AST is an *in vitro* phenomenon; it does not predict *in vivo* efficacy. Third, among susceptible antibiotics, a beta-lactam antibiotic, if possible, is usually recommended, especially in severe infections. Fourth, it is inappropriate to compare MICs among susceptible antibiotics because each antibiotic has its own PK, such as serum and tissue concentration, and different PK, such as time-/concentration-dependent or area under the curve-/MIC-dependent parameters. Fifth, if the AST results are reported as ≤, the antibiotics is effective and can be used, except in cases of an inability to get to the target site or an inability to achieve its target pharmacodynamic parameters. Sixth, the laboratory has more information or can perform additional testing for substitution to a cheap and oral-available antibiotic [121,122].

1. There are bactericidal and bacteriostatic antibiotics. Bactericidal antibiotics act on the inhibition of synthesis of the bacterial cell wall (beta-lactams or glycopeptides), membrane (daptomycin), or deoxyribonucleic acid (fluoroquinolones); bacteriostatic antibiotics act by protein synthesis inhibition, and include sulfonamides, tetracyclines, chloramphenicol, oxazolidinones, lincosamides, and macrolides. The distinction between bactericidal and bacteriostatic antibiotics may be changeable *in vivo*, influenced by growth conditions, bacterial density, test duration, and the extent of the reduction in bacterial numbers. MBC, time-kill curve, and serum bactericidal titer decide the bactericidal effect of antibiotics. It is only preferable to choose bactericidal agents in serious bacterial meningitis, endocarditis, or osteomyelitis [123]. Antibiotics can also be divided into broad (beta-lactams, amphenicols, tetracyclines, aminoglycosides, fluoroquinolones, and nitroimidazoles) or narrow spectrum agents (Gram-positive agents: glycopeptides, macrolides, oxazolidinones, lincosamides, and lipopeptides or

Table 9. Bacteria classified by Gram-staining (color), morphology, and other tests [115–118]

Gram-staining	Morphology	Other features for various tests					
Gram-positive bacteria (purple-colored staining due to retaining the crystal violet dye after washing with acetone or alcohol resulting from thick layer of peptidoglycan in the cell wall) are composed of thick layers of peptidoglycan, periplasmic space, and cytoplasmic membrane	Cocci	Aerobic	Catalase positive	Staphylococcus	Coagulase positive	Staphylococcus aureus	MRSA MSSA
					Coagulase negative	Novobiocin sensitivity positive	Staphylococcus epidermidis
						Novobiocin sensitivity negative	Staphylococcus saprophyticus
			Catalase negative	Streptococcus	Alpha	Optochin sensitivity and bile solubility positive	Streptococcus pneumoniae
						Optochin sensitivity and bile solubility negative	Viridans streptococci
					Beta	Bacitracin sensitivity and PYR status positive	Group A: Streptococcus pyogenes
						Bacitracin sensitivity and PYR status negative	Group B: Streptococcus agalactiae
					Gamma	Growth in 6.5% NaCl and PYR growth negative	Streptococcus bovis
				Enterococci		Growth in 6.5% NaCl and PYR growth positive	Enterococcus faecium Enterococcus faecalis
		Anaerobic	Peptostreptococci				
	Bacilli	Clostridium	Clostridium difficile				
			Clostridium botulinum				
			Clostridium tetani				
			Clostridium perfringens				
		Listeria monocytogens					
		Corynebacterium diphtheria					
		Bacillus	Bacillus anthracis				
			Bacillus cereus				
		Actinomyces					
		Nocadia					

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Table 9. Continued

Gram-staining	Morphology		Other features for various tests	
Gram-negative bacteria (pink-colored staining after washing with acetone or alcohol due to inability of retaining crystal violet resulting from thin layer of peptidoglycan in the cell wall) are composed of lipopolysaccharides, outer membrane, lipoprotein, and thin layers of peptidoglycan	Cocci	Diplococci	Neisseria	Neisseria meningitis Neisseria gonorrhoeae
	Bacilli	Enterobacteriaceae	Escherichia coli	
			Klebsiella pneumoniae	
			Salmonella dysenteriae	
			Yersinia	Yersinia pestis
				Yersinia enterocolitica
			Proteus mirabilis	
			Citrobacter	
			Serratia	
		Coccobacilli	Haemophilus influenzae	
			Bortedella pertussis	
			Brucella	
			Pasteurella	
			Acinetobacter baumanii	
		Others	Helicobacter pylori	
			Vibrio chlolerae	
			Campylobacter jejuni	
			Pseudomonas aeruginosa	
			Legionella pneumophila	
			Bartonella henselae	

MRSA: methicillin-resistant *Staphylococcu aureus*, MSSA: methicillin-susceptible *Staphylococcu aureus*, PYR: pyrrolidonyl arylamidase.

Gram-negative agents, such as polymyxins). However, antibiotics are usually classified by the mode of action mechanism (**Table 10**) [10,124].

The sixth revision of *Critically Important Antimicrobials for Human Medicine*, selected from the WHO in 2018, include gentamicin of the aminoglycosides, rifampin of the ansamycins, meropenem of the carbapenems and other penams, ceftriaxone (third-generation), cefepime (fourth-generation), ceftaroline (fifth-generation), and ceftobiprole (fifth-generation) of cephalosporins, fosfomycin of the phosphonic acid derivatives, vancomycin of the glycopeptides, tigecycline of the glycocyclines, daptomycin of the lipopeptides, azithromycin, erythromycin, and teithromycin of the macrolides and ketolides, aztreonam of the monobactams, linezolid of the oxazolidinones, ampicillin and piperacillin of the penicillins, amoxicillin-clavulanic acid of the penicillin-beta-lactamases inhibitors, colistin of the polymyxins, ciprofloxacin of the quinolones, and isoniazid of the anti-tuberculous antibiotics [125].

The order of the frequency of use in injectable antibiotics prescribed in the United States from 2004 to 2014 was β-lactams (65.3%), glycopeptides (9%), fluoroquinolones (8%), macrolides/ketolides (6%), aminoglycosides (5%), polymyxins (1%), trimethoprim/sulfamethoxazole (0.5%), tetracyclines excluding tigecycline (0.4%), and all other antibiotics including daptomycin, linezolid, and tigecycline (4.2%). Among the β-lactams prescribed, in detail, were cephalosporins (47.5%), broad-spectrum penicillins (36.5%), carbapenems (11.2%), narrow-spectrum penicillins (3.1%), and monobactams (1.7%). Therefore, cephalosporins ranked as the most commonly prescribed antibiotics [126].

2) Antibiotics that need therapeutic drug monitoring (TDM)

(1) General concept of TDM for antibiotics

TDM of antibiotics is applied for both maximizing the efficacy and minimizing the toxicity of antibiotic therapy in individual patients. There are drug and patient factors for the appropriate TDM. The antibiotic must include all of these: larger between-subject variability, small therapeutic index, an established concentration-effect (or toxicity), and obscure therapeutic response. Patients may show one of these factors, such as suspected drug interactions, suspected drug adverse effects/toxicity, suspected drug abuse, unexplained failed therapy, or suspected non-compliance. Antibiotics can be divided into time-dependent, concentration-dependent, and both time- and concentration-dependent drugs by the pharmacodynamic index for maximal efficacy of selected antibiotics. The time-dependent antibiotics include beta-lactams, carbapenems, linezolid, erythromycin, clarithromycin, and lincosamides. The concentration-dependent antibiotics include aminoglycosides, metronidazole, fluoroquinolones, telithromycin, and daptomycin. The time- and concentration-dependent drugs are azithromycin, tetracyclines, glycopeptides, and tigecycline [126].

Antibiotic PK is defined as what the human body does with the antibiotic during its complete cycle *in vivo* (absorption, metabolism, and excretion); antibiotic PD is defined as whether an antibiotic kills or inhibits the growth of the bacteria *in vivo* (dose-response curve). PK/PD is the optimal antibiotic activity achievable for the unbounded drug concentrations at the targeted infection site. The most common antibiotics that need TDM are glycopeptides, aminoglycosides, and chloramphenicol. In addition, piperacillin-tazobactam, meropenem, and ceftazidime (3rd generation cephalosporin) are frequently monitored beta-lactam antibiotics. Clinical timing of TDM is recommended during the very first dosing interval, and again 48 hours later. There are some difficulties if the antibiotic has a short half-life (such as 4–6 hours for beta-lactams and vancomycin) or a long total turnaround time for TDM in clinical practice [126,127].

(2) TDM for vancomycin and aminoglycosides

The most common antibiotics that need TDM are vancomycin and the aminoglycosides. In addition, physicians consider ordering TDM with beta-lactams, linezolid, teicoplanin, and voriconazole in critically ill patients [127,128].

① Vancomycin

Vancomycin is used for the treatment of Gram-positive infections, including MRSA. It is initiated from 25–30 mg/kg (rounded to the nearest 250 mg increment up to the maximum of less than 3 grams) intravenously, and is maintained at 15–20 mg/kg (rounded to the nearest 250 mg increment up to the maximum of less than 2 grams) intravenously every 8 or 12 hours. Normally, it is necessary to administer the drug 4-times daily to reach a steady state. Trough concentration is drawn 30 minutes before the 4th administration [129].

Renal function testing for preventing nephrotoxicity

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Table 10. Classification of antibiotics by their action mechanism and their coverage [10,124]

Mechanism of action	Class	Sub-class or antibiotic				Susceptible spectrum
Bacterial cell wall synthesis inhibition (through the blockade of cross linking by competitive inhibition of the transpeptidase)	Beta-lactams	Penicillins (Penams)	Narrow-spectrum	First generation beta-lactamase sensitive penicillins	Penicillin G Penicillin V	Gram-positive cocci, such as *Streptococci* Gram-negative rods, such as *Listeria* Gram-negative cocci, such as Neisseria Most anaerobes except *Bacteroides*
				Second generation beta-lactamase resistant penicillins (anti-Staphylococcal penicillins)	Methicillin Nafcillin Oxacillin Cloxacillin Dicloxacillin Flucloxacillin	Beta-lactamase or penicillinase-producing *Staphylococci* (but inactive against oxacillin-resistant *Staphylococci*)
			Broad-spectrum	Third generation amino-penicillins	**Ampicillin** Amoxicillin	*Streptococci, E. coli, P. mirabilis,* and *N. meningitis*
				Fourth generation antipseudomonal carboxypenicillins	Ticarcillin Carbenicillin	Gram negative bacteria (*Pseudomonas aeruginosa, Proteus*)
				Fifth generation ureidopenicillins	Piperacillin Azlocillin Mezlocillin	*Pseudomonas*
		Cephalosporins	First generation		Cefazolin (IV) Cephalexin (PO) Cefadroxil (PO) Cephalothin (IV) Cephradine (PO, IV)	MSSA, Streptococci, E. coli, P. mirabilis, and Klebsiella
			Second generation		Cefoxitin Cefaclor Cefuroxime Cefotetan	MSSA, Streptococci, E. coli, P. mirabilis, Klebsiella, and anaerobes
			Third generation		**Ceftriaxone** Cefotaxime Ceftazidime Cefpodoxime Cefixime Ceftibuten	*Enterobacteriaceae, Neisseria species,* and *H. influenza*
			Fourth generation		Cefpirome **Cefepime**	GNB with antibiotic resistance, such as beta-lactamase
			Fifth generation		**Ceftobiprole** **Ceftaroline**	MRSA and penicillin-resistant *Streptococcus pneumoniae*
		Beta-lactamase inhibitors	Beta-lactamase inhibitors with a beta-lactam core Beta-lactamase inhibitors with a diazabicyclooctane core Beta-lactamase inhibitors with other types of non-beta-lactam core		Clavulanic acid Sulbactam Tazobactam Avibactam Relebactam Vaborbactam	Beta-lactamase producing bacteria, such as MRSA, *Enterobacteriaceae*, *Haemophilus influenzae, Neisseria gonorrhoeae, Pseudomonas aeruginosa,* and *Mycobacterium tuberculosis*
		Carbapenems	Imipenem **Meropenem** Doripenem Ertapenem			Broad Gram-negative activity, especially *Enterobacteriaceae* but narrow Gram-positive activity

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Table 10. Continued

Mechanism of action	Class		Sub-class or antibiotic	Susceptible spectrum
		Monobactam	Aztreonam	Gram-negative bacteria, especially *Pseudomonas aeruginosa*
		Bacitracin		Topical application for Gram-positive bacteria
	Glycopeptides	**Vancomycin** Teicoplanin		All Gram-positive cocci, such as MRSA, MSSA, and Streptococci
	Cyclic lipopeptides	Daptomycin		Gram-positive cocci, multi-drug resistant Staphylococci, Enterococci, vancomycin-intermediate resistant Staphylococcus aureus, and vancomycin resistant Enterococcus
	Phosphonic acid derivatives	**Fosfomycin**		Urinary tract infection Due to Enterococci, MRSA, MSSA, and Staphylococcus epidermidis, and Gram-negative pathogens (Pseudomonas and E. coli)
Bacterial cell membrane disruption	Polymyxins	Polymyxin B and **E(Colistin)**		A last resort treatment of multi-drug resistant Gram-negative infections, such as E. coli, Klebsiella pneumoniae, and Pseudomonas aeruginosa
	Lipopeptides	**Daptomycin**		MRSA and VRE
Protein synthesis inhibition	Anti-30S ribosomal subunit	Aminoglycosides	**Gentamicin** Neomycin Amikacin Tobramycin Streptomycin	All Gram-negative bacilli
		Tetracyclines	Tetracycline Doxycycline Minocycline Demeclocycline Tigecycline	Gram-positive *Streptococci*, Gram-negative bacilli (*E. coli*), *Neisseria meningitis*, and atypicals
	Anti-50S ribosomal subunit	Macrolides	**Erythromycin** Azithromycin Clarithromycin Telithromycin	MSSA, Streptococci, *Neisseria meningitis*, and atypicals
		Chloramphenicol		Gram positive, negative and Rickettsia
		Lincosamide	Clindamycin	All Gram-positive cocci, such as MRSA, MSSA, Streptococci, and anaerobes
		Oxazolidinones	**Linezolid**	VRE and VRSA
		Streptogramins	Quinupristin/dalfopristin	VRE
DNA replication inhibitors	Fluoroquinolones (inhibition of DNA gyrase)	First generation	Nalidixic acid Cinoxacin Norfloxacin	GNB with minor Gram-positive bacteria
		Second generation	**Ciprofloxacin** Norfloxacin Enoxacin Ofloxacin Levofloxacin Lomefloxacin	MSSA and GNB
		Third generation	Gatifloxacin Sparfloxacin	Broad-spectrum

Table 10. Continued

Mechanism of action	Class	Sub-class or antibiotic		Susceptible spectrum
		Fourth generation	Moxifloxacin Gemifloxacin Trovafloxacin	MSSA, Streptococci, GNB (except Pseudomonas), anaerobes, and atypicals
	Nitronidazoles	Metronidazole		Anaerobes
RNA synthesis inhibitors	Ansamycins	**Rifampin**		Mycobacterium tuberculosis
	Actinomycin	Actinomycin D		Anticancer drug
Folic acid synthesis inhibitors	**Trimethoprim/sulfonamide**	Trimethoprim (inhibition of dihydrofolate reductase)		All Gram-positive cocci, most Gram-negative bacilli (except Pseudomonas), and N. meningitis
		Sulfonamides (inhibition of dihydropteroatte synthetase)	Sulfisoxazole Sulfadiazine	Broad-spectrum Toxoplasmosis Toxoplasmosis and malaria
	Pyrimethamine			
Inhibition of mycobacterial adenosine triphosphate (ATP) synthetase	**Isoniazid**			Mycobacterium tuberculosis

The antibiotics in bold are listed as critically important antibiotics for human medicine from the World Health Organization [130].

PO: per os, IV: intravenously, GNB: Gram-negative bacteria, MSSA: methicillin-resistant *Staphylococcus aureus*, MRSA: methicillin-susceptible *Staphylococcus aureus*, VRE: vancomycin-resistant *Enterococci*, VRSA: vancomycin-resistant *Staphylococcus aureus*.

should be monitored 3 times a week, and the frequency of the testing should be increased when vancomycin is combined in treatment with other nephrotoxic drugs, such as aminoglycosides or piperacillin-sulbactam. Vancomycin-induced nephrotoxicity is defined as a minimum of two or three consecutive documented increases (an increase of ≥ 0.5 mg/dL or ≥ 50% increase from the baseline) in the serum creatinine concentrations after several days of vancomycin therapy or a decrease in calculated creatinine clearance of 50% from the baseline on two consecutive days in case of an inability to find other causative factors with an alternative explanation [130].

The target trough concentration for uncomplicated soft infections is 10–15 μg/mL and for complicated infections, such as endocarditis, osteomyelitis, bacteremia, prosthetic joint infection, pneumonia, or meningitis, is 15–20 μg/mL. If the serum concentration is less or more than the targeted serum concentration, the total daily dosage should be increased or decreased using a change in the frequency (two to three times or vice versa) or dose (the dose increased or reduced by 25%). In patients with hemodialysis, 1,000 or 500–750 mg of vancomycin should be given after hemodialysis in cases of pre-hemodialysis serum concentration less than 10 or 10–25 μg/mL, respectively. Rapid intravenous infusion within 1 hour may increase the incidence of red man syndrome, hypotension, flushing, erythema, urticaria, pruritus, and cardiac arrest. Periodic monitoring for complete blood count is needed for the prevention of neutropenia and thrombocytopenia in prolongation of vancomycin therapy and in patients who are receiving concomitant medications which cause bone marrow suppression [129].

② Aminoglycosides

Parenteral aminoglycosides are administered two or three times daily with weight-based dosing (traditional intermittent aminoglycoside therapy) in patients with normal renal function. It is also recommended to give extended-interval aminoglycoside therapy once daily with a high dose. The best well-known adverse reaction is nephrotoxicity caused by proximal tubular epithelial cell injury and cochlear nerve injury, which is caused by ototoxicity as well [130].

The indication for high dose extended-interval aminoglycoside therapy is moderate to severe infections due to Gram-negative aerobic bacteria in immunocompetent patients, non-pregnant women, and those with urinary tract infections, intra-abdominal infections, respiratory infections, pelvic inflammatory disease, soft infections,

bacteremia, postpartum endometritis, and febrile neutropenia in malignancy. Contraindications include renal insufficiency with creatinine clearance less than 30 mL/minute, pregnancy, synergy with Gram-positive infections, ascites, and burns of over 20% of the body [130].

Gentamicin and amikacin is administered 5 and 15 mg/kg every 24 hours, respectively, in patients with normal kidney function for high-dose extended-interval therapy. The first TDM is required 6 to 14 hours after the initial dose. Peak serum concentration is obtained 1 hour after medication. Trough monitoring 30–60 minutes before administration should be checked in cases of abnormal renal function or suspicious high-dose extended-interval therapy. Maintenance random levels should be monitored once a week. Ototoxicity using audiometry should be observed if duration of therapy exceeds 2 weeks [130].

For traditional dosing, the initial dose of gentamicin and amikacin is 2 and 7.5 mg/kg, respectively. If they are administered four times a day, peak serum concentrations should be checked 30 minutes after the third administration, and trough serum concentrations are monitored 30–60 minutes before the fourth administration [130].

The target peak concentration of gentamicin is 4–6, 6–8, and 8–10 μg/mL for urinary tract infections, serious infections, and life-threatening infections, respectively. The target trough of gentamicin is less than 1–2 μg/mL. The target peak concentration of amikacin is 15–20, 20–25, and 25–30 μg/mL for urinary tract infections, serious infections, and life-threatening infections, respectively. The target trough of amikacin is less than 4–8 μg/mL [131].

3) Intravenous to oral antibiotic conversion

Conversion from intravenous to oral antibiotics after 2–3 days of therapy during hospitalization has advantages including lesser health care costs, earlier hospital discharge, and reduced intravenous catheter-related infections. This conversion can be divided into sequential, switch, or step-down therapy. Sequential therapy refers to replacing parenteral with oral medication of the same antibiotic with the same dosage. Switch therapy describes the conversion from intravenous to oral antibiotic equivalent within the same class and potency, but using a different antibiotic. Step-down therapy refers to the conversion from intravenous to oral antibiotic in a different class or in the same class where the frequency, dose, and spectrum of activity are not exactly the same [132,133].

Fluoroquinolones (levofloxacin and moxifloxacin) and macrolides (clindamycin) are the most common convertible antibiotics. In addition, the other appropriate and applicable antibiotics include tetracyclines (doxycycline and minocycline), sulfamethoxazole-trimethoprim, chloramphenicol, linezolid, and metronidazole [132,133]. There are various antibiotics which show excellent (over 90%) and good (between 60% and 90%) oral bioavailability (**Table 11**) [132,133].

Inclusion criteria for intravenous to oral conversion are ① patients with a well-functioning patent enteral route, ② patients receiving other oral medications, ③ improved signs and symptoms after administration of an intravenous antibiotic, ④ presence of an appropriate available oral form of antibiotic, and ⑤ an oral counterpart with proven comparable absorption and bioavailability. Exclusion criteria are ① patients with unreliable response to oral medication due to nausea and vomiting, inability to swallow, or who are unconscious, ② strict oral intake restriction due to a procedure or surgery, ③ gastrointestinal problems (obstruction, malabsorption, active bleeding, paralytic ileus, or diarrhea), ④ severe infectious diseases (meningitis, endocarditis, osteomyelitis, or sepsis) or documented *Pseudomonas* infection, ⑤ risk of seizure or aspiration, ⑥ shock, or ⑦ immunocompromised patients [133].

4) Antimicrobial combination therapy

Advantages of antibiotic combination therapy, compared to monotherapy, are ① avoiding resistance development in difficult-to-treat infections, such as tuberculosis or biofilm-associated infections treated with rifampin or fosfomycin, ② attenuating severe inflammation treated with macrolides, ③ inhibiting bacterial toxin production treated with clindamycin, and ④ acting synergistically and accelerating pathogen clearance in high bacterial loads treated with ampicillin and gentamicin against enterococci [134,135].

ESBLs are defined as plasmid-mediated enzymes, produced by a variety of GNB that can hydrolyze and inactivate beta-lactam antibiotics containing the oxyimino group, such as penicillins, oxyimino-cephalosporins, and oxyimino-monobactam, with the exception of cephamycins and carbapenems. Inactivating beta-lactam antibiotics by the ESBLs include third generation extended-spectrum cephalosporins, such as ceftazidime, ceftriaxone, cefepime, or cefotaxime, and oxyimino-monobactam, such as aztreonam [136,137].

The most common mechanism of resistance of GNB against beta-lactam antibiotics is production of beta-lactamase that can hydrolyze the antibiotics. The most com-

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Table 11. Various antibiotics which show excellent (over 90%) or good (60%–90%) oral bioavailability [132,133]

Antibiotics	Intravenous to oral conversion		Conversion methods
	Intravenous dosage	Oral dosage	
Excellent oral bioavailability over 90%			
Ciprofloxacin	200 mg every 12 hr	500 mg every 12 hr	-
Doxycycline	100–200 mg every 12 hr	The same dosage as intravenous administration	Sequential therapy
Levitiracetam	500 mg every 12 hr	The same dosage as intravenous administration	Sequential therapy
Levofloxacin	500 mg every 24 hr	The same dosage as intravenous administration	Sequential therapy
Linezolid	600 mg every 12 hr	The same dosage as intravenous administration	Sequential therapy
Metronidazole	500 mg every 12 hr	The same dosage as intravenous administration	Sequential therapy
Minocycline	200 mg every 12 hr	The same dosage as intravenous administration	Sequential therapy
Moxifloxacin	400 mg every 24 hr	The same dosage as intravenous administration	Sequential therapy
Good oral bioavailability between 60% and 90%			
Ampicillin	1 gram every 6 hr	250–500 mg every 6 hr	Sequential therapy
Azithromycin	500 mg every 24 hr	250–500 mg every 24 hr	Sequential therapy
Cefazolin	1 gram every 8 hr	Cephalexin 500 mg every 6 hr	Switch therapy
Cefotaxime	1grams every 8 hr	Ciprofloxacin 500–750 mg every 12 hr	Step down therapy
Ceftazidime	1–2 grams every 8 hr	Ciprofloxacin 500–750 mg every 12 hr	Step down therapy
Cefuroxime	500–750 mg every 8 hr	Cefuroxime axetil 250–500 mg every 12 hr	Switch therapy
Clindamycin	300–600 mg every 8 hr	300–450 mg every 6 hr	Sequential therapy
Erythromycin	500–1,000 mg every 6 hr	500 mg every 6 hr	Sequential therapy

mon ESBL-producing bacteria are *E. coli*, *K. pneumoniae*, *Enterobacter* species, *Proteus* species, and *Citrobacter* species, in order of frequency [138]. The beta-lactamases are divided into four classes according to molecular classification: A, B, C, and D enzymes. Class A, C, and D beta-lactamases are serine active-site hydrolases; class B beta-lactamases are zinc-metalloenzymes. These enzymes are produced by mutations that change the amino acid configuration around enzyme-active sites. However, they are inhibited by suicide inhibitors including 3 beta-lactamase inhibitors (clavulanic acid, sulbactam, and tazobactam) [139].

Clavulanic acid (clavulanate) is produced by the fermentation of *Streptomyces clavuligerus*, and is a naturally occurring powerful beta-lactamase inhibitor. The potassium salt of clavulanate is used in combination with beta-lactam antibiotics, such as amoxicillin or ticarcillin, under the brand name Augmentin® (GlaxoSmithKline Pharmaceutical, Mumbai, India) or Timentin® (GlaxoSmithKline Pharmaceutical, Mississauga, ON), respectively [140]. Sulbactam (penicillanic acid sulphone) is combined with ampicillin or cefoperazone, commercially available under the brand name Unasyn® (Pfizer, New York, NY) or Sulcefozone® (Pfizer), respectively [141]. Tazobactam is combined with ceftolozane or piperacillin, available under the brand name Zerbaxa® (Wellness Pharma International, Mumbai, India) or Zosyn® (Pfizer) [142]. The tazobactam/ceftolozane combination is approved for the treatment of complicated urinary infections and intraabdominal infections caused by carbapenemases-producer strains [14]. In addition, avibactam is combined with ceftazidime, commercially available under the brand name Avycaz® (Pfizer) [118]. There is also a new clinical trial with avibactam, ceftazidime, and metronidazole [143].

Bacterial programmed altruistic death, associated with the bacterial stress response to invading antibiotics, is considered to be 'a public good,' or beneficial to the other surviving bacteria, resulting in the 'eagle effect.' The eagle effect is a counter-intuitive phenomenon where bacteria appear to grow better in higher antibiotic concentrations [144]. On the contrary, beta-lactam and beta-lactamase inhibitor is a representative antibiotic combined therapy for enhancing the therapeutic effect of beta-lactam while avoiding altruistic death by the release of beta-lactamases. This is a never-ending war between human beings and bacteria.

Suggested antibiotic combination for suspected Gram-negative sepsis with *Pseudomonas* species includes a broad-spectrum beta-lactam and an aminoglycoside or a fluoroquinolone. Colistin combination has become a last resort treatment for MDRGNB infections. Combinations,

including an aminoglycoside, ampicillin/sulbactam, a carbapenem, colistin, or rifampin, are successfully used for MDR *Acinetobacter* species. Colistin-tigecycline and other combinations including an aminoglycoside, a carbapenem, colistin, fosfomycin, rifampin, or tigecycline are also used for carbapenemase-producing *Enterobacteriaceae*. Colistin increases the permeability of other antibiotics through the bacterial outer membrane by a detergent mechanism [145]. Combination antibiotic therapy for MDRGNB infections appears to be superior to monotherapy in mortality with the risk of increasing antibiotic resistance rates [15].

5) New generation of cephalosporins

The cephalosporins, β-lactam antibiotics, are the most commonly prescribed agents for both SAP and treatment. The merits of using cephalosporins in the clinical field include low rates of toxicity, a relatively broad spectrum of activity, and ease of administration. As use of cephalosporins are becoming widespread, drug resistance has also increased. The fifth generation cephalosporins have already been introduced for both expanding their spectrum and reducing bacterial resistance [146].

First-generation cephalosporins are effective against most Gram-positive cocci (MSSA and *Streptococci*, except MRSA) and some Gram-negative bacilli (*E. coli, P. mirabilis,* and *K. pneumoniae*). Second-generation cephalosporins have increased effectiveness against anaerobes. Third-generation cephalosporins, similar to the first generation cephalosporins, have developed a new power to kill *Enterobacter* species, *Serratia* species, *Citrobacter freundii*, *Aeromonas* species, *Proteus* species, *Providencia* species, and *Morganella morganii* (ESCAPPM) and Gram-negative cocci, while losing the ability to kill anaerobes of the second generation. They can also be divided into good activity excluding MSSA (ceftazidime) or poor activity against *P. aeruginosa* (cefotaxime and ceftriaxone). Fourth-generation cephalosporins have a similar effectiveness to third-generation cephalosporins, but with additional effectiveness against GNB, such as *Pseudomonas*. Fifth-generation cephalosporins are effective against MRSA and penicillin-resistant *S. pneumoniae* [146].

6) Antibiotics skin testing

It is also recommended to perform intradermal tests for an antibiotic prior to intravenous administration in order to prevent an immunoglobulin E-mediated immediate or delayed hypersensitivity reaction. The method for intradermal tests is not standardized and varies from hospital to hospital. The recommended volume and concentration of the injectate, size of the needle, and syringe are 0.02 mL of 1/100 dilution using a 27-gauge Tuberculin syringe. The diameter of the initial wheal just after injection is 5 mm. The time interval to immediate skin test reading is 15–20 minutes. The criteria for immediate positive skin testing varies ① if the wheal is 3–5 mm or more larger than initial wheal or becomes a double-sized wheal, or ② if the surrounding erythema is 15 mm or larger. The site commonly used for testing is on the volar aspect of the forearm. Negative control with saline is also recommended for use. A delayed positive reaction is determined when an erythematous induration or swelling exists at the injection site after 24 or 48 hours [147,148].

The recommended concentrations for skin testing for specific beta-lactam antibiotics are 10,000 IU/mL, 2–3 mg/mL for cephalosporin, and 20 mg/mL for semisynthetic penicillins, such as ampicillin, amoxicillin, and piperacillin [148].

About 10% of the U.S. population has allergies to beta-lactams. Cross-reactivity between penicillins and cephalosporins develops in about 2% of cases. A low-risk history for beta-lactams includes family history only, pruritus without rash, and isolated non-allergic gastrointestinal symptoms. Moderate-risk history includes urticaria or pruritic rashes and immunoglobulin E-mediated reactions. High-risk history includes anaphylaxis, positive skin testing, recurrent penicillin reactions, or hypersensitivity to multiple beta-lactams. Use of broad-spectrum antibiotics, instead of beta-lactams, leads to increased antibiotic resistance, resulting in increased MRSA, vancomycin-resistant Enterococcus, and *Clostridium difficile* infections [149].

7) Antibiotic stewardship program

An antibiotic stewardship program by infection specialists is already well-established in Korea, even though the opioid stewardship program by pain physicians is still in an initial state [150]. Thanks to restrictions on the misuse or abuse of broad-spectrum antibiotics, various types of antibiotic resistance have become reduced (**Table 12**) [151]. However, pain physicians should be concerned about the essential knowledge for novel antibiotics/antibiotic resistance and empirical antibiotic therapy within the first 24 hours or in a negative result from blood cultures.

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Table 12. Commonly used abbreviations for the explanation of antibiotic resistance [151]

Abbreviation	Definition
Organism-nonspecific abbreviations	
XDR	Extensively drug resistant Non-susceptibility to more than 1 antibiotics among 2 or less antibiotic categories
MDR	Multidrug resistant Non-susceptibility to more than 1 antibiotics among 3 or more antibiotic categories
PDR	Pan drug resistant Non-susceptibility to all antibiotics among all categories
Gram-negative-specific abbreviations	
ESBL	Extended spectrum beta-lactamase
CRE	Carbapenem-resistant Enterobacteriaceae
CPE	Carbapenemase-producing Enterobacteriaceae
Gram-positive-specific abbreviations	
MRSA	Methicillin-sensitive Staphylococcus aureus
MSSA	Methicillin-resistant Staphylococcus aureus
VISA	Vancomycin-intermediately resistant Staphylococcus aureus
VRSA	Vancomycin-resistant Staphylococcus aureus
VRE	Vancomycin-resistant Enterococcus
ESCHAPPM	Enterobacter species, Serratia species, Citrobacter freundii, Hafnia species, Aeromonas species, Proteus species, Providencia species. and Morganella species which have inducible beta-lactamase activity

Non-susceptibility refers to a resistant, intermediate, or non-susceptible result from antibiotic susceptibility testing.

CONCLUSIONS

As growing the field of IPM, the number of SSIs has become increased. In addition, patients with spinal infection, septic arthritis of the knee, hip, and shoulder, and cellulitis are frequently met in outpatient clinic. For the prevention of SSI in IPM, 18 do's and 7 don'ts are recommended from various guidelines.

The representative SAP in IPM is cefazolin as the first line, followed by clindamycin for beta-lactam allergy, vancomycin for beta-lactam allergy and known MRSA colonization, and teicoplanin for allergy to vancomycin. Diagnostic procedures include identification of causative bacterium from a blood culture, AST before empirical antibiotic therapy. Also, the serial measurement of the traditional (CRP, ESR, and WBC) and novel (procalcitonin, SAA, and presepsin) inflammatory markers is required.

Empirical antibiotic therapy is needed for the treatment of community-acquired pneumonia and infective endocarditis (immediately), sepsis (within 1 hour), bacterial meningitis (within 6 hours), as well as septic arthritis, diabetic foot infection or osteomyelitis, catheter-related urinary tract infection, and soft tissue infections (within 24 hours). Conversion from intravenous to oral administration during the definitive antibiotic therapy is performed through the sequential, switch, or step-down therapy, using antibiotics with excellent or good bioavailability. Antibiotics, such as vancomycin and aminoglycosides, require TDM. A never-ending war pitting antibiotic resistance against antibiotic combination therapy and a new generation of antibiotics is always evolving our understanding of antibiotics.

DATA AVAILABILITY

Data sharing is not applicable to this article as no datasets were generated or analyzed for this paper.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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