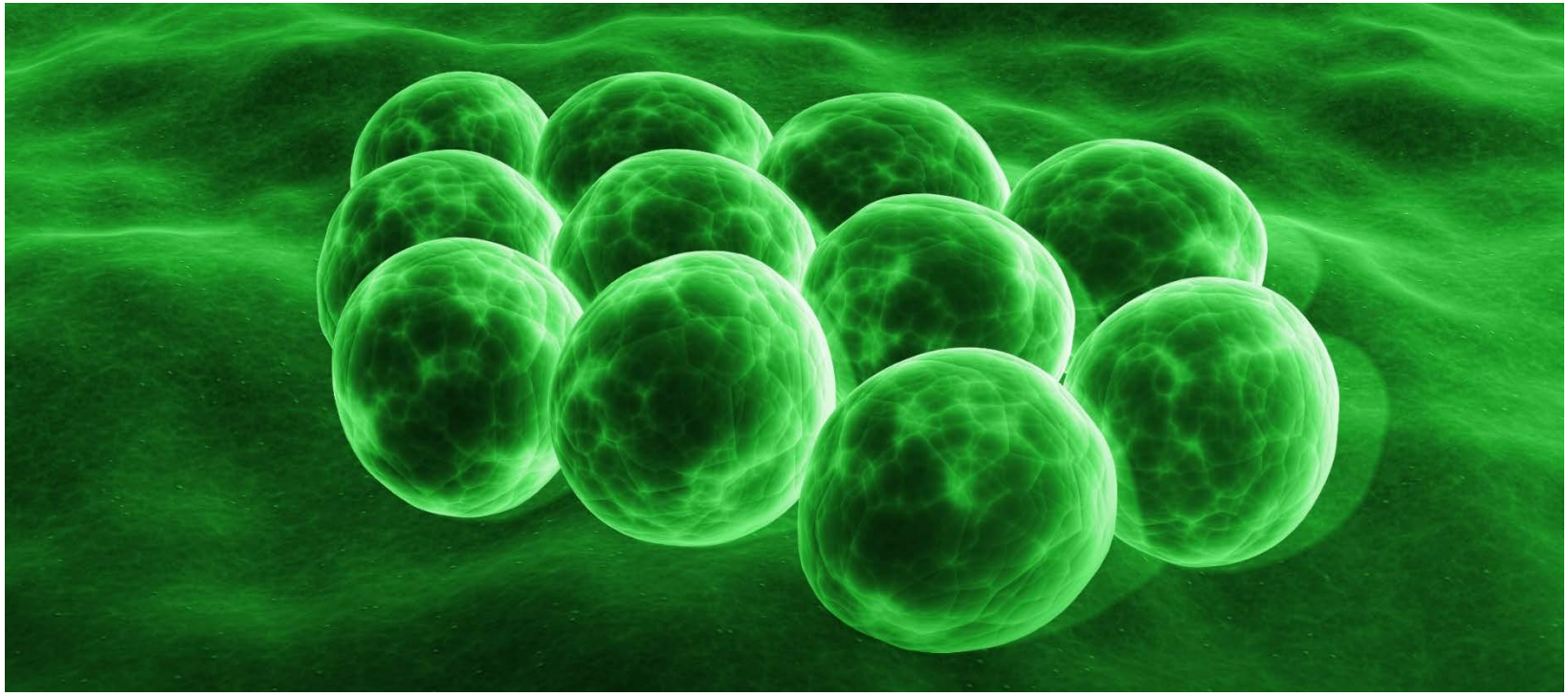

Introduction to Musculoskeletal Infection

In-person training for Distributor Sales Representatives

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Training objectives

At the end of this 30 minute training session you will:

- Understand the fundamentals of musculoskeletal infection; its cause, impact on patients and cost to the healthcare system
- Be aware of the most common types of musculoskeletal infection and the treatment options available to your surgeons
- Have gained a working knowledge of the key terms used in discussions about musculoskeletal infection

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Agenda

- Key terms
- Overview of musculoskeletal infection
- Surgical site infections
- Types of bacteria
- Biofilm
- Common orthopaedic infections
- Impact of musculoskeletal infection
- Treatment options
- Summary of key points

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Key terms

Acute infection: An infection that is present for less than 30 days

Antibiotic: A drug that kills or inhibits the growth of bacteria but not viruses

Antimicrobial: An agent that kills microorganisms or inhibits their growth

Bacteria: A large group of unicellular microorganisms

Biofilm: A complex community of bacterial cells enclosed in a self-produced extracellular matrix (ECM) that adhere to an inert or living surface

Chronic infection: A prolonged or persistent invasion of the body by pathogens, which indicates that biofilm is present

Debridement: A surgical technique where dead, necrotic and infected tissue is surgically excised

Drug-resistant infections: Infections that are resistant to antibiotics commonly used to kill infections caused by resistant strains of bacteria

ECM: Extracellular matrix is a polysaccharide coating formed by bacteria that contains host proteins acquired by the bacterial network

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Key terms

Gram Stain: A method used to differentiate two large groups of bacteria based on their cell wall constituents

Gram-negative bacteria: Have a cell wall composed of a thin layer of peptidoglycan that is located between an inner cell membrane and a bacterial outer membrane. Gram-negative bacteria take on the color of red/pink counterstain in the Gram's staining method

Gram-positive bacteria: Have a cell wall composed of a thick layer of peptidoglycan. Stain Gram-positive in Gram's method of staining because they retain the color of the crystal violet strain

HAI: Hospital acquired infection, which is a localized or systemic condition resulting from an adverse reaction to the presence of infectious agents or toxins that occurs in a healthcare setting

Inoculation: The introduction of an antigenic substance or vaccine into the body to produce immunity to a specific disease

MIC: Minimum inhibitory concentration is the lowest concentration of an antimicrobial that will inhibit the visible growth of a bacterium

Micro-organism: A microscopic organism that may exist as a single cell or in a colony of cells

Musculoskeletal infection: Invasion and multiplication of pathogenic microorganisms in the body

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Key terms

Non-union: A fracture that will not heal

Osteomyelitis: An infection of bone and bone marrow caused by bacteria

Peptidoglycan: A polymer made of amino acids and sugars that makes up the cell wall of bacteria

PJI: Periprosthetic Joint Infection is a postoperative complication that can occur following total hip or knee arthroplasty by bacterial inoculation at the time of surgery or through open draining wounds

Pathogen: Infectious microorganisms such as bacteria, viruses and fungi

Persister cells: Dormant variants of regular cells in microbial populations that are highly tolerant to antibiotics

Planktonic bacteria: Free-floating bacteria behave as unicellular organisms and can be easily identified

Polymicrobial: Disease state involving multiple species of multiple organisms

SSI: Surgical site infections, which are directly related to an operative procedure

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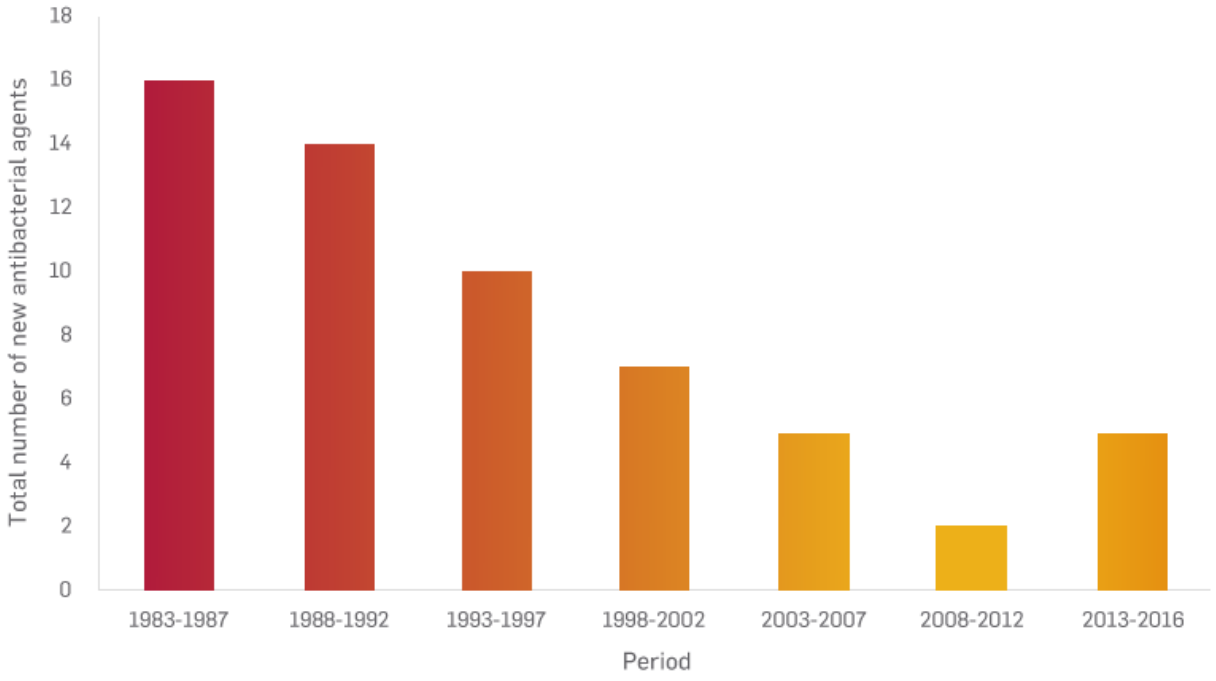
Overview of musculoskeletal infection

Rapid growth of antibiotic-resistant strains and biofilms continues to outpace the development of new antibiotics and antibiotic strategies[1,2]



- 50-60% of all hospital acquired infections are caused by antibiotic-resistant bacteria[3]
- The cost of antibiotic-resistant infections to the healthcare system is $21-$34 billion and 8 million additional hospital days[4]

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Occurrence of musculoskeletal infection

Surgical site infections (SSI)

- Significant risk associated with surgery
- Present a huge burden on hospital resources and annual expenditure
  - 1.7 million patients per year acquire an infection while in the hospital[3]
  - Account for approximately 23% of all hospital acquired infections[5]
  - Cost up to $10 billion annually in direct medical expenses[5]

- Identifying the micro-organisms that cause the SSI is essential to ensure the appropriate antibiotic and treatment strategies are selected[6]

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The cause of musculoskeletal infection

Bacteria

- Invasion of pathogenic unicellular micro-organisms
- Most common source for bacteria in hospitals is people[7]
- Differentiated into two distinct types

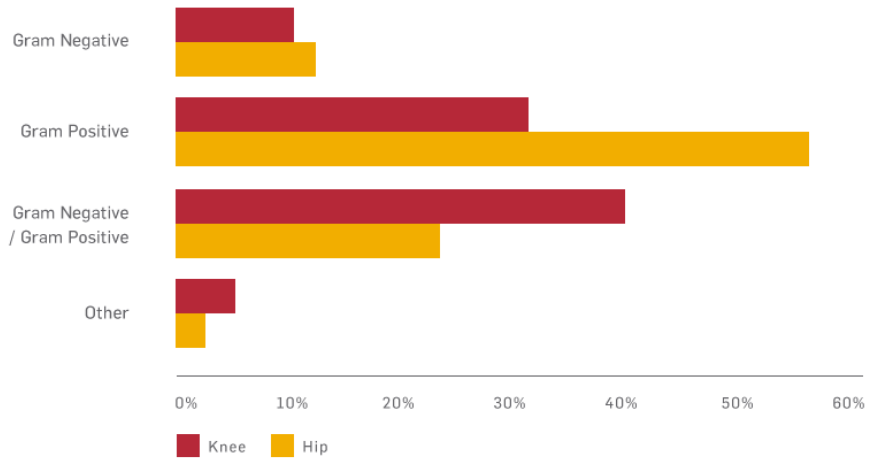
Gram-positive bacteria (77% of bacteria)[8]

- Found in skin particles and spread through the air or by direct contact with coated objects
- More receptive to antibiotics than Gram-negative bacteria

Gram-negative bacteria (23% of bacteria)[9,10]

- Found and transferred through direct contact with wet objects
- Resistant to most available antibiotics

Distribution of micro-organisms causing SSI[6]



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Gram's method of staining

Gram Stain

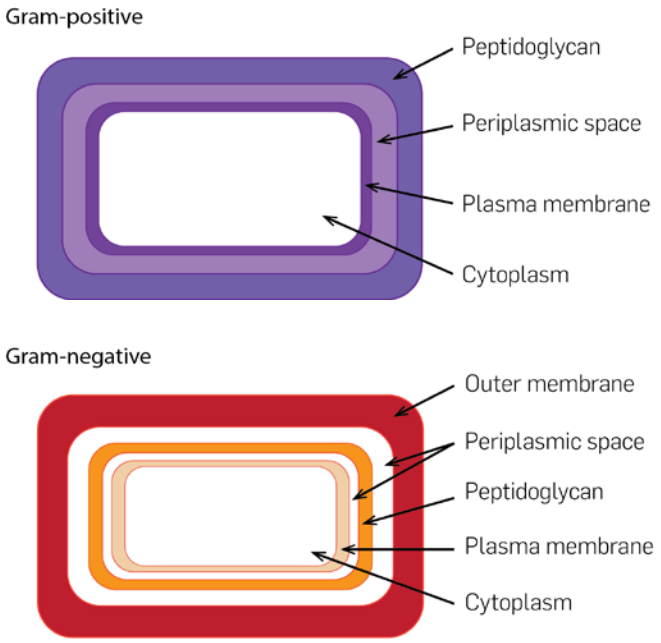
- A technique used to differentiate bacteria based on the difference in their cell wall properties
  - Distinguishes between Gram-positive and Gram-negative bacteria by coloring their cells violet or red

Gram-positive bacteria:

- Cell wall composed of a thick layer of peptidoglycan
- Stain Gram-positive: the cell wall retains the color of the crystal violet stain

Gram-negative bacteria:

- Cell wall composed of a thin layer of peptidoglycan, located between an inner cell membrane and a bacterial outer membrane
- Stain Gram-negative: the thin cell wall does not retain the crystal violet stain, and takes on the color of the red counterstain



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Minimum Inhibitory Concentration (MIC)

Overview

- MIC is the lowest concentration of an antimicrobial that will inhibit the visible growth of a bacterium
- MIC is used by clinicians to choose which antibiotics to administer for specific infections and to identify the clinically effective dose of antibiotic
  - Different antibiotics are used for Gram-positive, Gram-negative and polymicrobial infections
  - Polymicrobial infections often require more than one antibiotic to target all bacterial pathogens
- This is important because populations of bacteria exposed to an insufficient concentration of a particular drug or to a broad-spectrum antibiotic, can evolve resistance to those drugs
- MIC scores aid in improving outcomes for patients and preventing drug-resistant microbial strains evolving

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Planktonic bacteria vs. biofilm

Forms of bacteria in the body[11]

Planktonic bacteria

- Free-floating unicellular organisms
- Adhere to tissue or implant surfaces
- Easily identified
- Cleared by host's immune system or antibiotics

Biofilm

- Complex community of bacterial cells enclosed in a self-secreted extracellular matrix (ECM)
- Can firmly attach to inert or living surfaces
- Difficult to detect
- Resistant to immune system and antibiotics
- Cause of chronic disease

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Biofilm lifecycle

Timeline for biofilm development[12]

Biofilm stage	Timeline
Free-floating planktonic bacteria attach to a surface	minutes
Firmly attached microcolonies form	2-4 hours
Extracellular matrix develops	6-12 hours
Fully mature biofilm entering a dormant “persister” state	2-4 days
Biofilm re-forms after dispersion	24 hours

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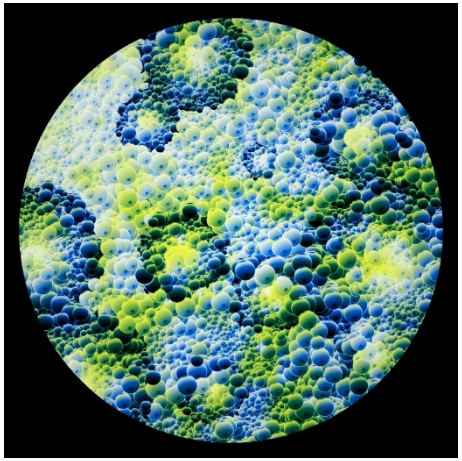
Biofilm

Properties of biofilm that lead to infection



- Limits the penetration of antimicrobials[13]
- pH differences allow some bacteria to become dormant while others remain active[13]
- Persister cells can withstand antibiotic attack and develop resistance to antibiotics[14]
- Difficult to detect and eradicate[13]
- Ability to avoid body's immune defenses[15]
- No methods or chemicals exist to dissolve a biofilm[13]

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Types of musculoskeletal infection

Common infections in orthopaedics

- Periprosthetic joint infection
- Osteomyelitis
- Infected non-unions
- Diabetic foot ulcers

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Periprosthetic joint infection (PJI)

Overview

- Postoperative complication following arthroplasty procedures
  - 1% of primary hip and knee arthroplasties become infected[10]
  - 16% of hip revisions are carried out due to infection[16]
  - 23% of knee revisions are carried out due to infection[16]
- Acute PJI:
  - Present for less than 30 days
  - Biofilm is not established and treatment is focused on implant preservation
- Chronic PJI:
  - A prolonged or persistent invasion of the body by pathogens, which indicates that biofilm is present
  - Two stage procedures are often required for the treatment of the infection and for revision arthroplasty

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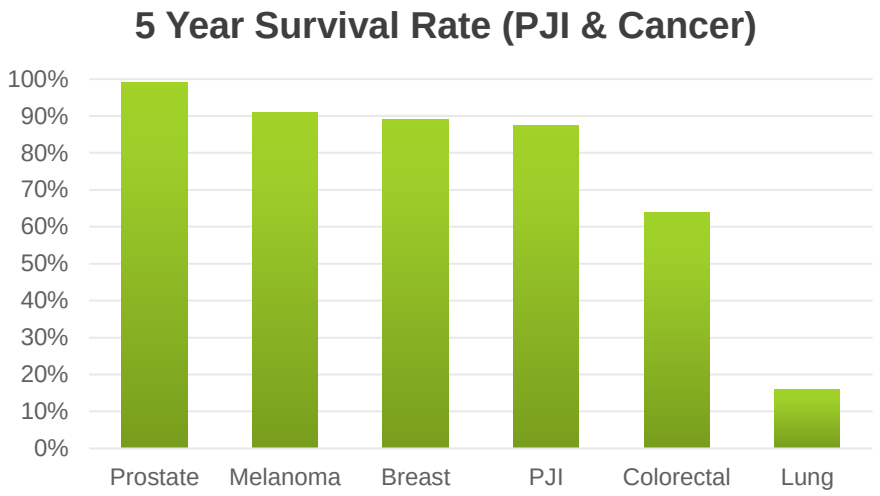
Periprosthetic joint infection (PJI)

Impact

- The annual hospital cost of infected revisions is estimated to exceed $1.6 billion by 2020[17]
- PJI revisions are associated with 5 times the risk of death compared to aseptic revisions[18]
- PJI has a lower 5 year survival rate than the three most common cancers[18]
  - 2018 data: The 5 year survival rate for Medicare patients with PJI was 67% after total hip arthroplasty and 72% after total knee arthroplasty[19]
  - 2013 data: The relative 5 year survival rate for patients with PJI was 87.3%[18]



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Acute PJI

Treatment example

- Debridement (used when joint components are not loose):
  - Incision and arthrotomy
  - Irrigation and debridement
  - Polyethylene insert exchange
  - Antibiotic therapy
- One-stage resection arthroplasty:
  - Incision and arthrotomy
  - Irrigation and debridement
  - Removal of cement and infected total knee components
  - Immediate implantation of new total knee components
  - Lavage and periprosthetic antibiotic therapy

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Chronic PJI

Treatment example – 2 stage resection arthroplasty

- Stage 1 - Focused on eradicating the infection:
  - Incision and arthrotomy
  - Resection of implant components
  - Irrigation and debridement
  - Use of antibiotic impregnated spacers to maintain space and provide stability
- Stage 2 - Occurs after infection is eradicated:
  - Incision and arthrotomy
  - Removal of antibiotic spacers
  - Irrigation and debridement
  - Implantation of revision arthroplasty components
  - Dead space and soft tissue management

Osteomyelitis

Overview

- Osteomyelitis is an infection of bone and bone marrow
- Can be acute or chronic
- Antibiotic therapy often fails
- Recurrence rates are between 20-30%[20]
- Common in infected non-unions and diabetic foot ulcers

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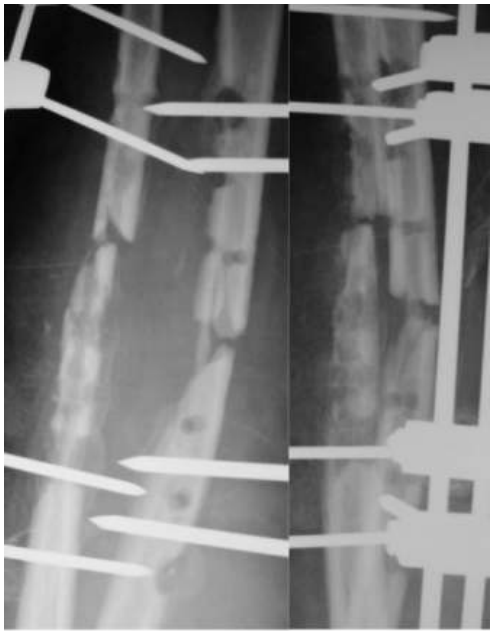
Infected non-unions

Overview

- Post-operative fracture that will not heal
- Caused by contamination by bacteria and failure of fixation
- Risk of infection depends on the type of fracture:
  - Closed fractures: Infection rates ≤ 5%[21]
  - Open fractures: Infection rates ≤ 50%[21]
- Complications:
  - Bone and soft tissue loss
  - Internal fixation loosening or breakage
  - Poor vascularity of the bony fragments
  - Osteomyelitis



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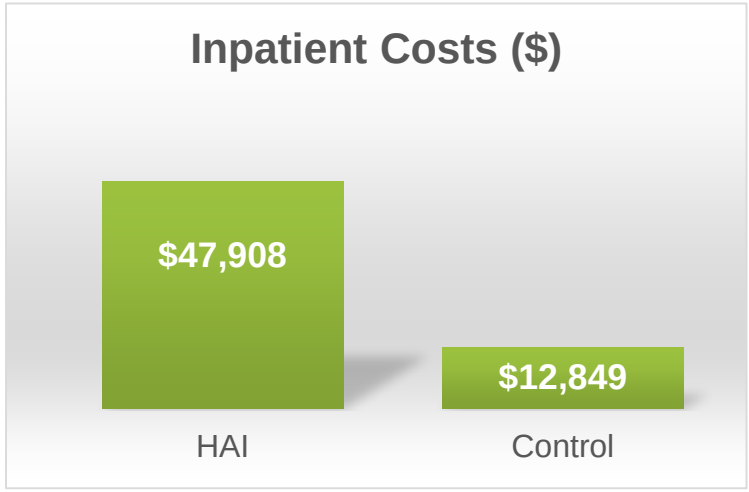
Infected non-unions

A study was conducted to explore the clinical impact and economic burden of hospital acquired infections (HAIs) in trauma patients[22]

- Increased mortality rates for patients with HAIs
- Longer hospitalization periods for patients with HAIs
- Higher costs for patients with HAIs



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Infected non-unions

Treatment example

- Removal of original hardware
- Debridement
- Revision stabilization of the fracture
- Supplemental bone grafting
  - Unmanaged spaces may contribute to infection
- Treatment of infection with antibiotics
- Two stage treatments may also be required to treat the infection and stabilize the non-union

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Diabetic foot ulcers

Overview

- A foot ulcer is an open sore or wound that is commonly located on the lower legs or bottom of the feet
  - 7.3 million people affected by diabetes in the U.S. have a lifetime risk of developing a foot ulcer[23,24]
- If untreated, a diabetic foot ulcer can become infected and lead to osteomyelitis
  - The prevalence of osteomyelitis ranges from 10-20%[25]
- Osteomyelitis is the leading cause of non-traumatic lower extremity amputations
  - 60% of lower extremity amputations are caused by osteomyelitis[25]

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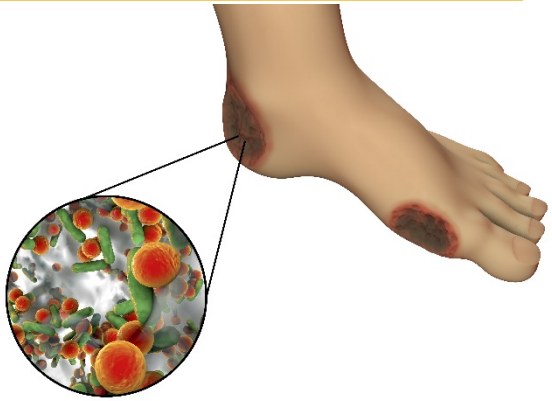
Diabetic foot ulcers with osteomyelitis

Impact

- Diabetic foot ulcers impose a tremendous medical and financial burden on our healthcare system
  - Patients require frequent emergency room visits, have increased hospital readmissions and require longer lengths of stay
  - Treatment costs are estimated to be ~$45,000 per patient[26]
  - Ulcer care adds $9-$13 billion to the direct yearly costs associated with diabetes[27]
- Remission rates for osteomyelitis can range up to 88%[25]
- ~50% of patients who have foot amputations due to diabetes die within five years[28]



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Diabetic foot ulcers with osteomyelitis

Treatment example

- Diagnosis of osteomyelitis
- Remove load from the ulcer site to redistribute force
- Debridement of infected bone
- Resection of compromised soft tissue
- Antimicrobial therapy
- Wound dressings with regular changes
- Increased healing rates and decreased length of antibiotic treatment have been reported with early surgical intervention for osteomyelitis[27]

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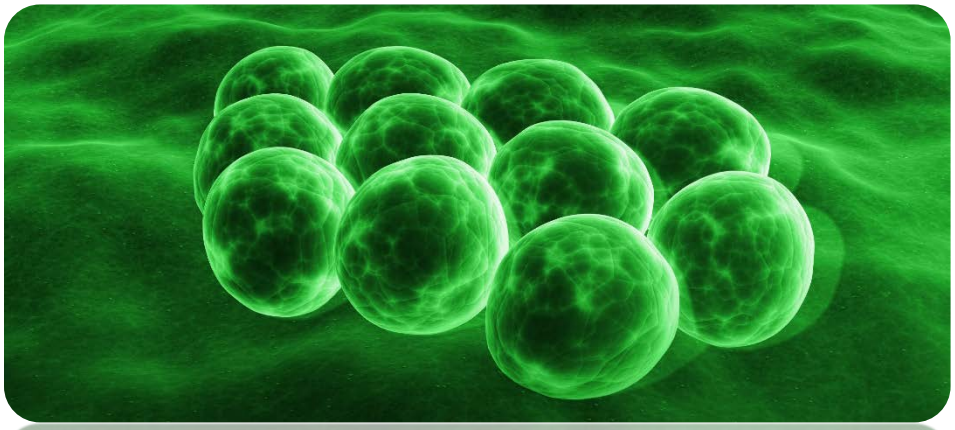
Musculoskeletal infection

Key points

- One of the biggest healthcare challenges of the 21st century
- Present a tremendous medical and economic burden on the healthcare system
- Represents a major cause of patient morbidity and mortality
- Care delivery is becoming increasingly challenging and complicated



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Power to transform™

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- Minimizing avoidable complications
- Improving outcomes
- Reducing costs

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Musculoskeletal infection

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Patents granted: EP 1390086 B1, US 8632796, CN ZL02809194.9, US 8496955, GB2367552, EP 1204599 B1, US 6780391, EP 1436019 B1, US 8563024, CN ZL02825134.2, EP 2594231 B1, US 8883063, CN ZL201210466117.X, GB2496710, EP 1954199 B1, US 8409251, EP 3058899 B1, US 10390954

Patents Pending: GB1502655.2, US 15/040075, CN 201610089710.5, GB1704688.9, EP 18275044.8, US 15/933936, CN 108619579A

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