Crossing Borders in Bone and Joint Infection Management

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Bone and joint infection has been a neglected field for years.
• Unpredictable results, anticipated bad prognosis, lack of standards, relatively low-incidence or even denial of septic complications, all contributed to relegate this condition in a largely unexplored and dangerous territory ...
• Adventuring here then required to a few pioneers in last decades to cross borders and frontiers, many of which still stand in front of us...
There is a land out there...

The very first border is to acknowledge the problem, avoiding superficial or blaming attitudes and, thus changing the way physicians, institutions, industry, patients and mass media may think.
There is a land out there...

*Homo sapiens idaltu* (approx 160,000-year-old) hominid fossils found in 1997 in Herto Bouri, Ethiopia.
There is a land out there...

Ancient Fossil bacteria (approx 1,000 million-year-old): Cyanobacteria from the Bitter Springs Chert, Australia.
Bone infections are with us since the very beginning...
1,900 / 1,600 B.C.
Infant pathologic specimens.
Crypt of the Ermita De la Soledad (Huelva, Spain)

DD most probable: Lack of vit. D, congenital syphilis and other treponematoses, tuberculosis, bacterial osteomyelitis
There is a land out there...

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■ HISTORICAL NOTE

A history of osteomyelitis from the Journal of Bone and Joint Surgery

1948 TO 2006

Osteomyelitis is one of the oldest diseases known. It took many years before the acute infection could be brought under control with antibiotics and chronic osteomyelitis remains difficult to manage. The modern history of the disease is reflected in the pages of the Journal of Bone and Joint Surgery.
2013
19 - Male
Haematogenous osteomyelitis
Colt ex: Strept group A
Senegal
2012
22 years old, student
Septic non-union of the femur after exposed fracture
Napoli (Campania)
2010
42 years old, policewoman
Post-surgical osteomyelitis of the calcaneus
Pantelleria (Sicily)
2012
50 years old, Italian armee officer
Septic cemented knee hinged prosthesis
Genova (Liguria)
... an unexplored land.

The next frontier are our dogmas and beliefs, the challenge of which will eventually really lead us to knowledge.
“When Columbus lived, people thought that the earth was flat. They believed the Atlantic Ocean to be filled with monsters large enough to devour their ships, and with fearful waterfalls over which their frail vessels would plunge to destruction.

Columbus had to fight these foolish beliefs in order to get men to sail with him.

He felt sure the earth was round.”

1632-1723
Anton van Leeuwenhoek
Delft, Holland

Using his handcrafted microscopes, he was the first to observe and describe single celled organisms, which he originally referred to as *animaluncules* ...
Bacteria in the Mouth

... an unexplored land.

First edition, Delft in Holland, 12 September 1683, to Francois Aston, Pag.11
"The little animals sitting in the white stuff on the teeth and molars (the plaque), could not endure the heat of my coffee (drink) and they were killed.

Like I have shown many times, that the little animals being in the water, died after some heating".

Letter nr. 75, 1692 on page 510-511
Alexander Ogston (1844-1929)
Aberdeen Royal Infirmary,
Scotland, United Kingdom.

Ogston, A. Ueber Abscesse.
... an unexplored land.

Ogston encountered a great deal of difficulty convincing the medical establishment of his observations on Staphylococcus.

The Aberdeen branch of the BMA, received his findings with disbelief.

The editor of the British Medical Journal stated at the time 'can anything good come out of Aberdeen ?'.

After a careful study of the evidence presented by Ogston, his contemporary, Joseph Lister agreed with his findings however, another peer, Watson Cheyne was still sceptical.
... an unexplored land.

Given this local skepticism, Ogston decided to present his discoveries to a surgical congress in Berlin.

Ogston delivered this presentation on abscesses in German which was then published.

He was subsequently made a 'Fellow' of the German Surgical Society despite his youth (36 years old).

Look for new pathways and companions.

Lateral thinking and sharing experience with other disciplines, while staying focused on our target, will allow us to cross the third border.
Look for new pathways and companions.

Juan de la Cosa

C. 1450 – C. 1510

Santoña, Spain
In 1847 Louis Pasteur, a young chemist freshly graduated from the prestigious Ecole normale supérieure, set to work on the problem posed by German physicist Eilhard Mitscherlich:

"why do sodium ammonium paratartrate and tartrate – two seemingly identical chemical substances – affect polarized light differently?"

Look for new pathways and companions.

1854-1915
Paul Ehrlich,
Strehlen, German Kingdom of Prussia
(now Poland)
Nobel, 1908

Original drawing, 1900

“selective toxicity”

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“After he showed that dyes react specifically with various components of blood cells and the cells of other tissues, he began to test the dyes for therapeutic properties to determine whether they could kill off disease-causing microbes. He met with promising results using methylene blue to kill the malaria parasite.”

https://www.chemheritage.org/historical-profile/paul-ehrlich
Look for new pathways and companions.
Build bridges.

Crossing the fourth border requires the ability to favor translational research and to lower barriers to new technologies, with an approach that should be similar to that adopted for “rare diseases”.
Build bridges.

Source: CAPA - Centre for Aviation and OAG (n.b. Direct flight cities are in red, connecting flights [e.g. code shares] in blue).
Review

From in vitro to in vivo Models of Bacterial Biofilm-Related Infections

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Diabetic Mouse Model of Orthopaedic Implant-Related Staphylococcus Aureus Infection

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Tool kit for explorers.

To explore this land you need to be well equipped for complex and sometimes risky procedures.

A tool kit that needs continuous training and update.
Tool kit for explorers.

On 5 March 1496 Henry VII gave Giovanni Caboto and his three sons letters patent with the following charge for exploration:
Tool kit for explorers.
Tool kit for explorers.
Tool kit for explorers.
Tool kit for explorers.
Tool kit for explorers.
Crossing borders is worthless, if you don’t write down the map.

Take your time to set the standards, share and validate protocols, tracing the way for the next explorer to come.
Write down the map.

Martin Waldseemuller was a German printer and map maker. In 1507, he printed a huge world map. The map included North and South America. The two continents were drawn long and narrow. He used information from Columbus, Cabot, and Vespucci to make the map.
Write down the map.

The Cierny-Mader Classification

- **Medullary** Osteomyelitis - Infection confined to medullary cavity.
- **Superficial** Osteomyelitis - Contiguous type of infection. Confined to surface of bone.
- **Localized** Osteomyelitis - Full-thickness cortical sequestration which can easily be removed surgically.
- **Diffuse** Osteomyelitis - Loss of bone stability, even after surgical debridement.
Bone and joint infections in adults: a comprehensive classification proposal

Table 2  The seven items of the “Seven-Item Comprehensive Classification System” of bone and joint infections

<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>Etiopathogenesis</th>
<th>Anatomo-pathology</th>
<th>Host type/age</th>
<th>Microorganism</th>
<th>Bone defect</th>
<th>Soft tissue defect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td>Early</td>
<td>Rachis</td>
<td></td>
<td>A(_{a,c,i})</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Subacute</td>
<td>Delayed</td>
<td>Hand</td>
<td></td>
<td>B(_{a,c,i})</td>
<td>2</td>
<td>cm(^2) B</td>
</tr>
<tr>
<td>Chronic</td>
<td>Late</td>
<td>Long bones</td>
<td></td>
<td>C(_{a,c,i})</td>
<td>3A, 3B, 3C</td>
<td>cm(^2) B +</td>
</tr>
<tr>
<td></td>
<td>Trauma</td>
<td>Stage 1</td>
<td></td>
<td>Mixed flora and/or multiresistant</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vasculopathy/neuropathy</td>
<td>Stage 2</td>
<td></td>
<td>Mycobacterium</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Temporary implant</td>
<td>Stage 3</td>
<td></td>
<td>Fungi</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ICS classification</td>
<td>Stage 4</td>
<td></td>
<td>Negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Type I</td>
<td>Foot</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Type II</td>
<td>Joint</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Type III</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Permanent implant</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Honor previous explorers.

Remember those that became “stars” and those who remained unknown, but yet gave their silent contribution to cross the next frontier.
Honor previous explorers.

1843-1910
Robert Koch
Nobel, 1905

1866 – 1955
Albin Lambotte

1861 – 1912
Alessandro Codivilla

1866 – 1955

1910 – 2002
Hans-Wilhelm Buchholz

1921 – 1992
Gavril Abramovich Ilizarov

1947 – 2013
George C. Cierny III
Honor previous explorers.

The Nobel Prize in Physiology or Medicine 1945 awarded jointly to

Sir Alexander Fleming
St. Mary's Hospital in London

Ernst Boris Chain
Oxford University

Sir Howard Walter Florey
Oxford University

"for the discovery of penicillin and its curative effect in various infectious diseases"
1869 -1915
Vincenzo Tiberio
Medical officer of the Medical Corps of the Italian Navy
and physician at the University of Naples.
Published a paper in 1895 on the antibacterial power of some extracts of mold.

His work anticipated the discovery of the drug penicillin by Alexander Fleming 35 years later.

At the time, his work was disregarded as coincidence and received no further study.

1869 - 1915
Vincenzo Tiberio
Medical officer of the Medical Corps of the Italian Navy and physician at the University of Naples.
Detection of Prosthetic Hip Infection at Revision Arthroplasty by Immunofluorescence Microscopy and PCR Amplification of the Bacterial 16S rRNA Gene

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Honor previous explorers.

**TABLE 2.** Bacteria detected from culture-positive retrieved prosthetic hip implants by culture, IFM, and bacterial 16S rRNA gene detection and associated tissue inflammatory response

<table>
<thead>
<tr>
<th>Sample no.</th>
<th>Bacterium(a) isolated</th>
<th>Tissue infiltration by inflammatory cells (score)(^a)</th>
<th>IFM result</th>
<th>16S rRNA gene detection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>PMN(^b)</td>
<td>LYM(^c)</td>
<td>MAC(^d)</td>
</tr>
<tr>
<td>1</td>
<td><em>S. epidermidis</em></td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td><em>S. epidermidis</em></td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td><em>S. aureus</em></td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td><em>S. capitis</em></td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td><em>S. epidermidis</em></td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td><em>S. hominis</em></td>
<td>0</td>
<td>0</td>
<td>2</td>
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<tr>
<td>7</td>
<td><em>S. epidermidis</em></td>
<td>1</td>
<td>1</td>
<td>3</td>
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<tr>
<td>8</td>
<td><em>S. epidermidis and S. hominis</em></td>
<td>0</td>
<td>2</td>
<td>3</td>
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<tr>
<td>9</td>
<td><em>S. epidermidis and S. hominis</em></td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>10</td>
<td><em>S. epidermidis and S. capitis</em></td>
<td>2</td>
<td>2</td>
<td>2</td>
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<tr>
<td>11</td>
<td><em>P. acnes</em></td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>12</td>
<td><em>P. acnes</em></td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>13</td>
<td><em>P. acnes</em></td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>14</td>
<td><em>P. acnes</em></td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>15</td>
<td><em>P. acnes</em></td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>16</td>
<td><em>P. acnes</em></td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>17</td>
<td><em>P. acnes</em></td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>18</td>
<td><em>P. acnes</em></td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>19</td>
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<td>NS</td>
<td>NS</td>
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<tr>
<td>20</td>
<td><em>P. acnes</em></td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>21</td>
<td><em>P. acnes</em></td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>22</td>
<td><em>P. acnes</em></td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>23</td>
<td><em>S. hemolyticus and P. acnes</em></td>
<td>1</td>
<td>1</td>
<td>1</td>
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<tr>
<td>24</td>
<td><em>Micrococcus sp. and P. acnes</em></td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>25</td>
<td><em>S. epidermidis and P. acnes</em></td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Tunney et al. 1999
Be positive – Be propositive

Painting by Emanuel Gottlieb Leutz. Columbus Meets Ferdinand of Aragon and Isabella of Castile.
Be positive – Be propositive

EBJIS – Industry Cooperative Task Force

Improving the CE Certification Process

EBJIS International Certification of Bone and Joint Infection Centers Project

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World is big, you are small.

Then cross the final border: your self-confidence.

Bacteria were before you and will be after you, so...

remain humble.
On his second visit to Jamaica, in 1503, Columbus was shipwrecked and remained in St. Ann’s Bay for a year.
World is big, you are small.

Klebsiella pneumoniae
Multi-R

Pseud. Aeruginosa
Multi-R

Acinetobacter baumanii
Multi-R

Providencia stuartii
<table>
<thead>
<tr>
<th>Component</th>
<th>Timeframe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteria</td>
<td>&gt; 2,000,000,000 yrs</td>
</tr>
<tr>
<td>Homo sapiens sapiens</td>
<td>200,000 “</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>70 “</td>
</tr>
<tr>
<td>Antibiotic-loaded cement</td>
<td>50 “</td>
</tr>
<tr>
<td>Biofilm understanding</td>
<td>40 “</td>
</tr>
</tbody>
</table>

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**Surface sandblasted titanium**

*Courtesy Prof. L. Drago*

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Thank you and ...

There is a land out there...
an unexplored land.
So, look for new pathways and companions,
Build bridges,
Have your tool kit for explorers ready,
Write down the map.
Honor previous explorers,
Be positive – Be propositive
and remember...
World is big, you are small...

Arrivederci!