
XIX
CONGRESSO
NAZIONALE AMD
Roma, 29 maggio - 1 giugno 2013
Rome Marriott Park Hotel

Diagnostica e terapia antibiotica nelle infezioni del paziente con diabete

Edoardo Carretto

S.C. Microbiologia
IRCCS Arcispedale Santa Maria Nuova, A.O. Reggio Emilia

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- **'The microbe is nothing, the terrain is everything'.** Louis Pasteur,1895, on his deathbed, quoting Claude Bernard's motto.

- Diversi deficit immunologici sono noti nei pazienti con diabete, principalmente relativi a un'alterata funzione dei polimorfonucleati con riduzione dell'efficacia della fagocitosi e dell'attività antimicrobica (killing batterico).

Milioni di pubblicazioni scientifiche a carattere infettivologico…

Acinetobacter spp. can also cause peritonitis in patients undergoing continuous ambulatory peritoneal dialysis. It is difficult to be certain that all such episodes are nosocomial, but technique failure and diabetes mellitus are the main underlying risk factors. The mean duration of risk factors before the

How should the risk of complications be assessed in a primary care patient with LRTI? 'Patients with an elevated risk of complications should be monitored carefully and referral should be considered. In patients over 65 years of age the following characteristics are associated with a complicated course: presence of COPD, diabetes or heart failure, previous hospitalization in the past year, taking oral glucosteroids,

The presence of the following comorbid conditions was documented: diabetes mellitus, heart failure, chronic obstructive pulmonary disease (COPD), hepatic dysfunction, renal failure (as indicated by the necessity for dialysis), history of cerebro-

Table 1 Etiology in 50 patients with Fournier's gangrene

Etiology	Patients	%
Anal Abscess	31	62
Thrombosed hemorrhoid	4	8
Strangulated inguinal hernia	1	2
Unknown	14	28

with vertebral osteomyelitis often have underlying medical conditions (e.g., diabetes mellitus, cancer, chronic renal disease) or a history of intravenous drug use.[12] Back pain

one comorbidity. Diabetes mellitus (DM) was the most common comorbidity associated with FG and was present in 17 patients (34%) at the time of admission. In

Diabetes mellitus (DM) is known as an important risk factor for surgical site infection (SSI) in spine surgery. It is still unclear however which DM-related parameters have stronger influence on SSI. The

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- Il paziente con diabete ha una maggiore predisposizione a sviluppare eventi infettivi sia sistemici, che localizzati:
  - sepsi
  - piede diabetico, osteomieliti
  - infezioni di ferita (lenta risoluzione)
  - polmoniti (altri fattori predisponenti)
  - altre patologie: mucormicosi, parodontopatie, pielonefriti, colangiti enfisematose, IVU severe in pazienti con vescica neurologica…

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PLOS | ONE

Diabetic Patients with Severe Sepsis Admitted to Intensive Care Unit Do Not Fare Worse than Non-Diabetic Patients: A Nationwide Population-Based Cohort Study

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Table 6. Previous published works comparing the outcomes particularly the mortality rate between diabetics and nondiabetics with sepsis or severe infection.

Authors	Published year	Mortality rate (DM vs. non-DM)	Study Settings
Carton JA et al.	1992	Overall mortality and bacteremia-related mortality were similar in both groups.	Prospective study of all adult pts with bacteremia admitted to a large Spanish teaching hospital
Kornum JB et al.	2007	Mortality among diabetic pts was greater than that among other pts: 19.9 vs. 15.1% after 30 days and 27.0 vs. 21.6% after 90 days, corresponding to adjusted 30- and 90-day MRRs of 1.16 (95% CI 1.07–1.27) and 1.10 (1.02–1.18).	Population-based cohort study of adults with a first-time hospitalization for pneumonia
Moutzouri AG et al	2008	The mortality in non-diabetic septic pts was 22.5% and in septic diabetics was 34.3%.	40 pts suffering from severe sepsis, 12 pts suffering from diabetes and 24 diabetic pts with severe sepsis were enrolled.
Stoeckle M et al	2008	In-hospital mortality rate was similar in the two groups (18% vs. 14%).	During a 4-year period 71 diabetic and 252 non-diabetics with bloodstream infection were included.
Esper AM et al.	2009	People with DM were less likely to develop acute respiratory failure (9% vs. 14%, p<0.05) and more likely to develop acute renal failure (13% vs. 7%, p<0.05).	Using the National Hospital Discharge Survey US, sepsis cases from 1979 to 2003 were integrated with DM prevalence from the CDC Diabetes Surveillance System.
Kofteridis DP et al	2009	People with DM had longer fever (median 4.5 vs 2.5 days; P<.001), longer hospitalization (median 10 vs 7 days; P<.001), and greater mortality (12.5% vs 2.5%; P<.01) than controls.	88 pts aged 65 and older with DM and 118 controls without DM, matched for age and sex, hospitalized with acute pyelonephritis
Peralta G et al.	2009	Mortality among diabetic and non-diabetic pts was not different [7.2% vs. 8.2%, RR 1.13; 95% CI (0.67–1.9); p = 0.39].	Retrospective cohort study to investigate prognosis in pts with Enterobacteriaceae bacteremia.
Stegenga ME et al	2010	Mortality was equal in diabetic and nondiabetic pts (31.4% vs. 30.5% after 28 days).	Retrospective analysis of a previously published study.
Schuetz P et al.	2011	The mortality rate was 4.3% (95% CI 3.9% to 4.8%) and similar in diabetic and nondiabetic pts (4.1% versus 4.4%; absolute risk difference 0.4%; 95% CI −0.7% to 1.4%).	3 independent, observational, prospective cohorts from Emergency Department pts with sepsis from 2 large US tertiary care centers
Chang C et al	This study	Diabetic pts with severe sepsis complicated with acute organ dysfunction do not fare worse with an adjusted HR of 0.979 (0.908–1.055).	Nationwide population-based retrospective cohort study in pts with severe sepsis requiring ICU admission

CI: confidence interval; DM: diabetes mellitus; HR: hazard ratio; ICU: intensive care unit; Pts: patients.

doi:10.1371/journal.pone.0050729.t006

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Emocoltura

Because the information provided by a positive blood culture can have such important prognostic and therapeutic implications, blood cultures should be performed for patients with new fever, even when the clinical findings do not strongly suggest a noninfectious cause.

Guidelines for evaluating new fever in critically ill adult patients (ISDA e SCCM), CID, 1998

- Obtain appropriate cultures before starting antibiotics provided this does not significantly delay antimicrobial administration
- Obtain two or more BCs
- One or more BCs should be percutaneous
- One BC from each vascular access device in place > 48 hrs
- Culture other sites as clinically indicated
- Sample any source of infection, if safe to do so

Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock 2008. *Crit Care Med*. 2008;36(1):296-327

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- Criticità della procedura "emocoltura"
  - adeguata disinfezione con clorexidina 2%
  - raccogliere più set emocolturali (aerobi-anaerobi) sia per raccogliere un adeguato volume di sangue, che per differenziare microrganismi contaminanti da veri patogeni (stafilococchi coagulasi negativi)
  - in caso di CVC, prelevare sempre anche un campione da vena periferica – valutare il tempo di positivizzazione per la diagnostica di sepsi catetere-correlata
  - inviare immediatamente al laboratorio, quindi iniziare una terapia antibiotica empirica (a largo spettro, basata sulla realtà epidemiologica oppure sulla supposta porta di ingresso del microrganismo)

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TABLE 2. Etiology of Pneumonia by Study Group

Variable	Patients With DM (n=516) No. (%)		Patients Without DM (n=1891) No. (%)		P
Streptococcus pneumoniae	201	(39)	792	(41.9)	0.24
Pneumococcal bacteremia	45	(9.4)	206	(10.9)	0.15
Haemophilus influenzae	20	(3.9)	97	(5.1)	0.29
Aspiration pneumonia	42	(8.1)	139	(7.4)	0.57
Legionella pneumophila	27	(5.2)	91	(4.8)	0.63
Staphylococcus aureus	1	(0.2)	15	(0.8)	0.14
Gram-negative bacilli	13	(2.5)	37	(2)	0.48
Pseudomonas aeruginosa	9	(1.7)	24	(1.3)	0.41
Atypical agents	12	(2.3)	63	(3.3)	0.31
Other	13	(2.5)	64	(3.4)	0.39
No pathogen identified	196	(37.9)	619	(32.7)	0.11

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Diagnosis and Management of Community-Acquired Pneumonia in Adults

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TRACY L. LEMONOVICH, MD, *University Hospitals Case Medical Center, Cleveland, Ohio*

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendations	*Evidence rating*	*References*
In patients with clinically suspected CAP, chest radiography should be obtained to confirm the diagnosis.	C	12
Evaluation for specific pathogens that would alter standard empiric therapy should be performed when the presence of such pathogens is suspected on the basis of clinical and epidemiologic clues; this testing usually is not required in outpatients.	C	12
Mortality and severity prediction scores should be used to determine inpatient versus outpatient care for patients with CAP.	A	22-24
All patients with CAP who are admitted to the intensive care unit should be treated with dual therapy.	A	28
Prevention of CAP should focus on universal influenza vaccination and pneumococcal vaccination for patients at high risk of pneumococcal disease.	B	12, 35-37

CAP = community-acquired pneumonia.

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afpsort.xml.

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Table 3. Recommended Diagnostic Testing in Patients with Suspected Community-Acquired Pneumonia

Indication	*Blood culture*	*Sputum culture*	Legionella *urine antigen test*	*Pneumococcal urine antigen test*	*Other*
Admission to intensive care unit	✓	✓	✓	✓	Endotracheal aspirate if intubated
Alcohol abuse	✓	✓	✓	✓	
Asplenia	✓			✓	
Cavitary infiltrates	✓	✓			Fungal and tuberculosis cultures
Chronic severe liver disease	✓			✓	
Leukopenia	✓			✓	
Outpatient therapy ineffective		✓	✓	✓	
Pleural effusion	✓	✓	✓	✓	Thoracentesis and pleural fluid cultures
Positive *Legionella* urine antigen test result		✓			
Positive pneumococcal urine antigen test result	✓	✓			
Recent travel (within past two weeks)			✓		
Severe obstructive lung disease		✓			

Adapted with permission from Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis. *2007;44(suppl 2):S40.*

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Table 7. Empiric Therapy for Community-Acquired Pneumonia

Patient group	*Initial therapy*
Previously healthy outpatients; no antibiotic use in past three months	A macrolide or doxycycline
Outpatients with comorbidities* or antibiotic use in past three months†	A respiratory fluoroquinolone (levofloxacin [Levaquin], gemifloxacin [Factive], or moxifloxacin [Avelox]), or a beta-lactam antibiotic (high-dose amoxicillin, amoxicillin/clavulanate [Augmentin], or cefpodoxime) plus a macrolide‡
Inpatients, non-ICU	A respiratory fluoroquinolone, or a beta-lactam antibiotic plus a macrolide
Inpatients, ICU	A beta-lactam antibiotic (ceftriaxone [Rocephin], cefotaxime [Claforan], or ampicillin/sulbactam [Unasyn]), plus azithromycin (Zithromax) or a respiratory fluoroquinolone§
Special considerations	
Risk factors for *Pseudomonas* species	A beta-lactam antibiotic (piperacillin/tazobactam [Zosyn], cefepime, imipenem/cilastatin [Primaxin], meropenem [Merrem], or doripenem [Doribax]), plus either ciprofloxacin (Cipro) or levofloxacin *or* The above beta-lactam antibiotic plus an aminoglycoside and azithromycin *or* The above beta-lactam antibiotic plus an aminoglycoside and an antipneumococcal respiratory fluoroquinolone
Risk factors for methicillin-resistant *Staphylococcus aureus*	Vancomycin or linezolid (Zyvox)
Influenza virus	Oseltamivir (Tamiflu) or zanamivir (Relenza)

ICU = intensive care unit.

**—Chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancy; asplenia.*

†—*Antibiotic from a different class should be used.*

‡—*Also recommended in regions with a rate of high-level macrolide-resistant* Streptococcal pneumoniae *of greater than 25 percent.*

§—*For patients allergic to penicillin, a respiratory fluoroquinolone plus aztreonam (Azactam) are recommended.*

Adapted with permission from Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis. *2007;44(suppl 2):S45.*

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IDSA GUIDELINES

2012 Infectious Diseases Society of America Clinical Practice Guideline for the Diagnosis and Treatment of Diabetic Foot Infections[a]

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Piede diabetico: epidemiologia

- Estrema variabilità negli studi → preanalitica!
- Sebbene sia considerabile EBM la maggiore sensibilità e specificità dei campioni profondi (agobiopsie o biopsie), alcuni studi continuano a considerare gli isolamenti da tamponi superficiali

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Piede diabetico: microrganismi isolati

Diabetes & Metabolism 34 (2008) 87–95

Review

Diabetic foot osteomyelitis

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Received 24 August 2007; accepted 6 September 2007
Available online 31 January 2008

Table 1
Microbiological aetiology of osteomyelitis of the foot in diabetic patients (values given as percentage of total number of microorganisms)

Microorganisms	Ref [14]	Ref [15]	Ref [18]	Ref [19]
Aerobic gram-positive cocci				
Staphylococcus aureus	26	40	47	31
Coagulase-negative staphylococci	25	10	11	50
Streptococci	12	45	61	27
Enterococcus sp.	8	30	28	8
Other	5	10	–	–
Aerobic gram-negative bacilli				
Enterobacteriaceae	11	55	14	20
Pseudomonas sp.	3	5	11	15
Anaerobes	6	60	15	4
Polymicrobial	–	70	83	–
Organisms (*n*)/bone samples (*n*)	1.54	–	2.25	–

Original Research

Role of bone biopsy specimen culture in the management of diabetic foot osteomyelitis

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International Journal of Surgery 9 (2011) 214–216

Table 1
Organisms isolated in ulcer swab and bone biopsy specimen culture in diabetic foot ulcer patients with suspected osteomyelitis.

Organism	Swab (%) (n = 288)	Bone biopsy (%) (n = 264)
Staphylococcus aureus	66(22.9)	82(31.1)
Pseudomonas species	50(17.4)	50(18.8)
Acinetobacter baumannii	41(14.2)	35(13.3)
Escherichia coli	37(12.8)	37(14.0)
Proteus species	34(11.8)	25(9.5)
Klebsiella species	26(9.1)	19(7.2)
Streptococcus pyogenes	18(6.2)	8(3.0)
Enterobacter species	6(2.1)	2(0.8)
Others	10(3.5)	6(2.3)

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DIABETES/METABOLISM RESEARCH AND REVIEWS
Diabetes Metab Res Rev 2008; 24(Suppl 1): S66–S71.
Published online 8 April 2008 in Wiley InterScience (www.interscience.wiley.com) DOI: 10.1002/dmrr.828

REVIEW ARTICLE

New developments in diagnosing and treating diabetic foot infections†

- Progressivo aumento degli isolamenti di MRSA (30-50%). Grandi differenze da centro a centro.
- MRSA correla con colonizzazione nasale.
- MRSA NON correla con fattori di rischio noti (ospedalizzazione, abuso antibiotici).
- Aumento di frequenza negli isolamenti di Gram negativi MDR (correlati con fattori di rischio).

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Epidemiologia locale

	2010	2011
• Stafilococco aureo	43 (11 MR)	30 (12 MR)
• Stafilococchi coag. neg.	14	=
• *Morganella/Proteus/Providencia/Serratia*	12	15
• *Pseudomonas aeruginosa*	8	4
• *Escherichia coli*	8	13
• *Klebsiella pneumoniae*	6	=
• Altri Gram negativi	9	8
• Altri Gram positivi	1	7

Si ringrazia il dott. Carlo Capatti per l'insostituibile supporto…

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- **Utilizzare sistemi classificativi di gravità, da specificarsi nella richiesta (es PEDIS Grade o IDSA Infection Severity …)**
- Grado 1: assenza di segni o sintomi di infezione
- Grado 2: presenza di infezione, in assenza di terapia antibiotica recente

↓

NO ESAMI MICROBIOLOGICI

- Grado 2: presenza di infezione con terapia antibiotica recente
- Gradi 3-4 (infezioni moderate o severe)

↓

INDAGINI MICROBIOLOGICHE

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- Il prelievo di tessuto deve sempre essere eseguito attraverso biopsia o curettage.
- È indispensabile che la ferita venga adeguatamente pulita.
- L'esecuzione di tamponi superficiali non è consigliabile e, in particolare, **non sono accettabili** per l'analisi microbiologica tamponi da lesioni non curettate e, soprattutto, tamponi eseguiti da tramiti fistolosi.
- Il rischio è quello di isolare principalmente microrganismi commensali con successivo abuso di antibiotici.

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Cosa fare?

- **Tampone superficiale: da evitarsi** laddove possibile
  - diagnostica correttamente il 75% delle infezione di cute e tessuti molli e solo il 30% dei patogeni causa di osteomielite. Se eseguito, dovrebbe essere seminato come metodica dei quattro quadranti e refertato semiquantitativamente
- **Osteomielite**: agobiopsia percutanea, exeresi chirurgica o punch biopsy
- **Sempre inviare campione in anatomia patologica** (evidenza istologica di osteomielite)
- **Tampone nasale nello screening –** gestione del paziente a cadenza semestrale?

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Come fare?

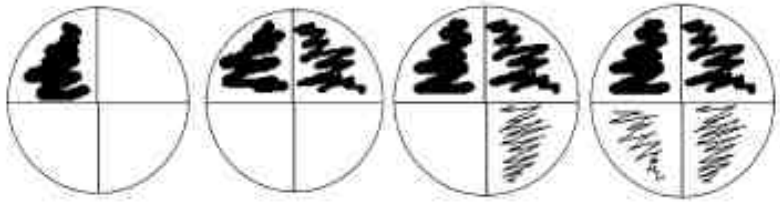
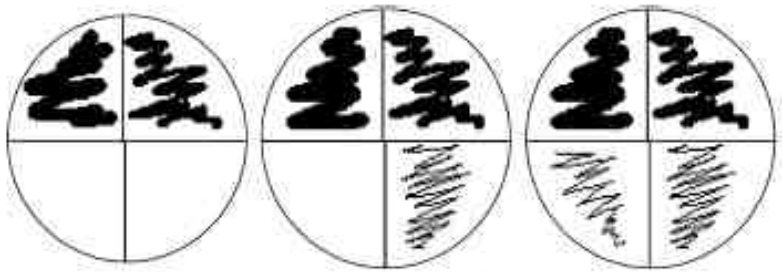
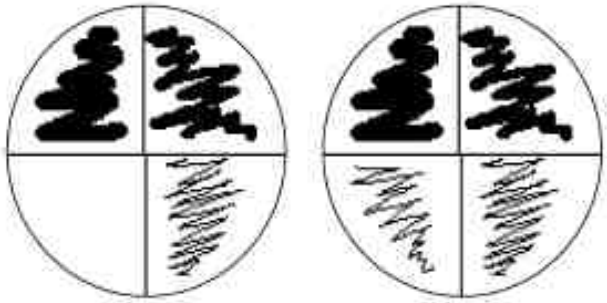
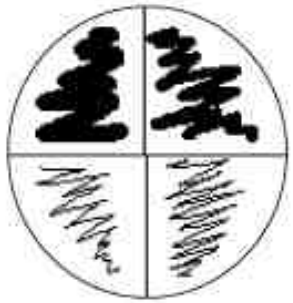
- **Tampone superficiale:** far pervenire in laboratorio più rapidamente possibile. Se breve tempo, alcuni possono essere seminati anche in anaerobiosi
- **Curettage o scraping del tessuto** alla base dell'ulcera con l'utilizzo di una curette o una lama da bisturi sterile: sensibilità maggiore.
- Altre metodiche accettabili per il prelievo sono **l'aspirazione mediante ago sterile e siringa** di secrezioni purulente della ferita oppure **l'utilizzo di cateteri venosi** da introdursi in tramiti fistolosi e lavaggio con fisiologica

Come fare?

Agobiopsia: scaricare il frustolo in una provetta sterile con tappo a vite, aggiungendo 1 goccia di fisiologica. Far pervenire in laboratorio più rapidamente possibile: se breve tempo, può essere seminata anche in anaerobiosi.

Punch bioptico - biopsia ossea: deporre il materiale (cubetto di 0,5 cm di lato) in una provetta sterile con tappo a vite, aggiungendo 1 goccia di fisiologica. Far pervenire in laboratorio più rapidamente possibile: se breve tempo, può essere seminata anche in anaerobiosi.

Table 3 Sensitivity and specificity for semiquantitative analysis of wound swab when different diagnostic thresholds (levels of growth) are used

Diagnostic threshold	Level of growth	Sensitivity, %	Specificity, %
Threshold A		100	37
Threshold B		100	63
Threshold C		79	90
Threshold D		26	99

IDMI

Systematic review of methods to diagnose infection in foot ulcers in diabetes

S. O'Meara, E. A. Nelson, S. Golder*, J. E. Dalton, D. Craig*, C. Iglesias on behalf of the DASIDU Steering Group (see footnote for members)

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Alternative (es. prelievi che non possono essere recapitati in Laboratorio tempestivamente): utilizzo di sistemi per anaerobiosi

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Fase post-analitica

- Tanto più attenta e appropriata è la fase pre-analitica, tanto più è agevole la post-analisi
- Tamponi:
  - più di tre microrganismi devono essere refertati come flora polimicrobica
  - gli SCN e i corinebatteri non in monoflora devono essere segnalati senza identificazione di specie, né antibiogramma
- Agobiopsie – materiali bioptici a punch o dopo exeresi:
  - più di tre microrganismi devono essere refertati come flora polimicrobica
  - per tre o meno isolati va fatta identificazione e antibiogramma

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Verso il futuro?

- Tecniche specialmente evocate nella diagnostica delle osteomieliti
- Uso di terreni selettivi
- Tecniche molecolari quali PNA-FISH o real-time-PCR (?)
- Microarrays per identificazione e caratterizzazione dei geni di resistenza (?)

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Back to the future!

- "Our germs isolation rate doubles whenever a physician or nurse calls for specimen collection information."

  modified from C. George Ray (St. Louis University Medical Center, St. Louis, Mo)

- "Ideally, sent the specimen, not a swab of the specimen."

  Karin McGowan (Children's Hospital, Philadelphia, Pa)

- "If identification is an issue, forget the swab and get some tissue."

  Michael Saubolle (Phoenix, Arizona)

- "As more of our testing becomes available by molecular methods, clinicians and laboratorians need to learn when to probe, when to amplify, and when to colture."

  Lisa L. Steed (Medical University of South Carolina, Charleston SC)

- "We can have the highest-skilled technologists using the most sensitive and sophisticated assays, but we can't make us for a poor specimen."

  Wallace H. Greene (M.S. Hershey Medical Center, Hershey, Pa)

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Piede diabetico: opzioni terapeutiche

- Grado 0 – Nessuna terapia
- Grado 1 – eziologia più frequente: Gram positivi.
  - Somministrazione per os di beta-lattamine coniugate, meno attivi i fluorchinoloni. Alternative, attive anche su MRSA, vecchie molecole quali tetracicline e cotrimoxazolo.
  - Possibile combinazione con terapia topica, possibile gestione domiciliare. Durata del trattamento: 7-14 giorni sino alle 4 settimane in forme a lenta risoluzione.

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Piede diabetico: opzioni terapeutiche

- Grado 2 – differenti microrganismi. La terapia deve essere orientata sull'isolamento microbiologico e sui test di sensibilità.
  - Se MSSA ancora amoxi-clavulanato (efficace anche su anaerobi). Se G-, cefalosporine di III generazione. Se infezioni miste, utilizzare fluorchinoloni (se attivi) oppure tigeciclina, attiva anche su MRSA. Possibile utilizzo di carbapenemici, vancomicina e piperacillina/tazobactam se MDRO
  - Terapia parenterale con shift alla via orale appena possibile. Valutare se possibile gestione domiciliare. Durata del trattamento: 7-21 giorni sino alle 6 settimane in forme a lenta risoluzione.

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Piede diabetico: opzioni terapeutiche

- Grado 3 – differenti microrganismi. La terapia deve essere orientata sull'isolamento microbiologico e sui test di sensibilità.
  - Se MSSA oxacillina e.v.. Se G-, cefalosporine di III generazione. Se infezioni miste, utilizzare fluorchinoloni (se attivi) oppure tigeciclina, attiva anche su MRSA. Possibile utilizzo di carbapenemici, vancomicina e piperacillina/tazobactam se MDRO.
  - Terapia parenterale con shift alla via orale appena possibile. Valutare se possibile gestione domiciliare. Durata del trattamento: 14-28 giorni sino alla risoluzione clinica.

E.C. 2013

Piede diabetico: opzioni terapeutiche

- Osteomielite – differenti microrganismi. La terapia deve essere orientata sull'isolamento microbiologico e sui test di sensibilità.
  - Terapia parenterale con shift alla via orale appena possibile. Durata del trattamento variabile:
    - 2-5 giorni se amputazione,
    - 7-21 giorni se presenza residua di tessuti molli (no osso),
    - 4-6 settimane se revisione estesa con residui ossei
    - oltre i 3 mesi se non opzione chirugica.

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Mucormicosi

- Più frequenti le forme a carico dei seni nasali, più rare quelle cutanee, polmonari o a carico del SNC.
- Patologie potenzialmente devastanti.
- Avvisare il laboratorista: sono muffe a crescita rapidissina (apprezzabili a 24 ore), spesso considerate contaminazioni ambientali.
- Ridotte opzioni terapeutiche: amfotericina B liposomiale, 5 mg/kg, non indicati azoli o echinocandine.