Becoming a Wound Care and Antibiotic Resistance Hero

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Disclosures & Disclaimers

Nothing to disclose

No conflicts of interest

The views expressed here are solely those of the author, and are not be construed as official or representing the United States Army or the Department of Defense.
Learning Objectives

• At the conclusion of this presentation, the lectures participants will be able to:

1. Explain the biofilm concept and how it pertains to treatment decisions involving wound care, wound infections, and hardware or device infections

2. Formulate an approach to becoming a “wound care hero” by restating the six imperatives for managing difficult wounds

3. Apply pharmacokinetic/pharmacodynamic dosing principles to maximize antibiotic effectiveness and minimize collateral damage
Learning Objectives

4. Summarize the antibiotic resistance crisis and identify specific measures that can be taken to mitigate antibiotic resistance, such as limiting duration of therapy

5. Explain how surveillance can be used to mitigate resistance, improve patient safety, and reduce healthcare costs
Causes of Wounds

• Post operative
• Infected wounds; ischemic ulcers; neuropathic ulcers; ulcers caused by systemic dx = RA, IBD, lupus; pressure ulcers / bed sores
• Bite, burns, radiation
• Post traumatic
Wound Care

• Scope and Definitions
  • Chronic = 30 days not responsive
  • 8 million US patients at any given time
  • 16 million Diabetics in US – 15% will develop foot ulcer
  • Half of all nontraumatic lower extremity amputations occur in DM
  • Foot ulcers precede 85-90% amputations
  • 1 yr. after a toe 20% undergo an ipsilateral amp
  • 1-3 yrs. after initial amp, 50% undergo contralateral amp then in the next 5 yrs., 50% will undergo a second contralateral amp
Scenario 1

- 63 yo wf IDDM retinal neuro a-v insufficiency
- Thermal burn in shower
- Dry dressings Keflex and Cipro
- 1.25 ABI 3+ LE edema b/l
- Loss of cortex and fx of calcaneus
- Surface cults Klebs and skin flora
- Deep cults P. aeruginosa
- Cefipime cipro; freq. sharp debridement; wound vac, (negative pressure wound TX and offloading)
Scenario 1

• Modified compression stocking
• **Weekly debridement**
• Apligraf
• Healed after 6 weeks
Wound Vac

- Not over eschar
- Not over necrotic
- Must be nicely granulating- nothing else
- Some experts say no role in diabetic foot ulcers
Scenario 2

- 80 yo female MVA knee hematoma
- Afib DM, HTN
- Knee effusion
- Eschar over patella –
- levo & vanc for 2 weeks
- 4 wks later
  - Drainage arthrocentesis – cx neg.; treated empirically w ctx and wet to dry saline
  - Caveat need 3 times a day- at least (hurts)
  - Freq. sharp debridement (can also hurt)
Mesh infection – Scenario 3

• 62 yr. old male w/ gastric bypass
• Permacol mesh
• R-sided abd wall abscess contiguous w mesh
• Aspirate grew MRSA
• TX w/ daily collagenase (good for necrotic not eschar) sharp debridement
• Dapto for 8 weeks- - watch for MIC creep
• Collagenase then zinc oxide daily
• Then trim/sulf suppression bid
- Abdominal binder used
- Prisma – (non adherent absorbant alginate dressing)
- Petroleum impregnated gauze
- Wound curettage and debridement 2x weekly
- Healed after 6 months
- Point is: dressing nuances and debridement
- And make sure follow vanc levels (15-20) and MICs and dapto MICs
Case 4: Incisional hernia repair

- 67 y/o female w- Prolene mesh 8 yrs. prior
- Presented w fistula and fluid collection
- Grew Strep, Enterobacter, Candida albicans
- Removed mesh and graft
- TX w wound vac changed 2-3 times week
- Ceftrix, flucon for 2 weeks
- Make sure sponge went into undermined areas
- Healed w split thickness skin graft
- Proper placement of sponge is crucial
Case 5

- IDDM male 84 severe PVD, stents, fem pop bypass,
- Gangrene of R 4\textsuperscript{th} toe
- Amputation of toe followed by a ray amputation w/ flap closure
- Referred for non healing
- Cx: Proteus mirabilis and Klebs
- Given cipro
- HBO not an option b/c of co-morbidities
- TX w/ wound vac and sharp debridement
Case cont’d

• But healing stagnated and had exposed bone
• Next set of cultures grew: *C. albicans* and MRSA
• Treated w/ acetic acid wet to dry & off-loading
• Darco wedge shoe important part of therapy
• Keeps pressure of area – opposite of what is needed for heal ulcers
• Linezolid, flucon, and Cipro
Case cont’d

- No osteo on **plain film** – issues w/ sensitivity but OK in a wound w/ bone exposure – some say useless, some say if it’s normal it’s really normal
- Regranex and saline once a day – spread on granulating surface
- Apligraf 50-60% heal w/ one graft and other 3rd need a second Apligraf
Summary Take Home Points

- Very large wounds – not amenable to Apligraf
- Biggest is 2 petri disease
- Can only be used in good granulation
- Superficial cultures re of limited utility
- Must get rid of necrotic tissue for wounds to heal
- Synthetic skin vs real skin
  - Venous stasis and diabetic FDA indications for synthetic
Summary points

• If probe to bone have about 70-80% chance you are dealing w/ underlying osteo

• Electrical stimulation – never used for wound healing, but used for bone regeneration

• Total contact casting or walking boot used for maximum offloading
Summary Points

• Utilize dressings that don’t have to be changed every day, i.e. foam/polymer
  – For saline wet to dry – if possible try gel
• Utilize grids, photos, and assessment sheets
• Measured compression stockings (11 different sizes)
• Practice good infection control
• Use antibiotics wisely
Pitfalls

• Forgetting about nutrition, circulation & drainage
• Over-reliance on antibiotics
  – When to stop antibiotics?
  – Do not use surveillance culturing to stop abx: it’s a clinical decision (appearance, behavior, ESR, CRP, imaging, procalcitonin?)
  – Using ertapenem for pseudomonas
    • (Attractive b/c once a day)
  – Underdosing , not checking levels
Becoming a Wound Care Hero

1. TX venous stasis with compression NOT ABX
   Two sizes: too big or small; one size fits none- measure
2. Biopsy unresponsive or misbehavers
3. Maximize blood flow and nutrition
4. Debride debride and then debride
5. Learn nuances of chemicals, orthotics, grafts
6. Use antibiotics wisely
7. Recognize a lost cause from the start and refer for amputation
   1. Surgeons, scalpels, ER docs defibrills, FPs- relationship
The Biofilm Concept

- Well known in industrial & environmental microbiology - first
- 1979-1982 pacemaker infection and 2\textsuperscript{nd} bacteremia tx’d unsuccessfully w/ 6+ weeks antibiotics
- Now universally accepted
- Not planktonic and not simple accretions

There are five stages of biofilm development (see illustration at right):
- Initial attachment:
- Irreversible attachment:
- Maturation I:
- Maturation II:
- Dispersion:
The Biofilm Concept

- Intelligent, responsive populations with integrated signaling and communications
  - Transfer resistance elements 1000x faster than among planktonic
  - Chemical, electrical and information
- 15% bacterial mass and 85% slime/polysaccharide matrix
The Biofilm Concept

• Urine + catheter+ few bacteria = coating in 8 hrs., by 48-72 hrs. ~200 cells thick
• Embedded cells (200 cells deep) have MBC 1000x that of planktonic analogs
• Clinical symptoms and course:
  – Planktonic break off, cause symptoms
  – Antibacterial therapy suppresses, recurrence following cessation of antibiotics
  – Damage cause by inflammatory response
Biofilm Concept

• Remove a chunk of biofilm and culture = no growth (only if shedding planktonic do you get a positive culture)

• In ortho cx has sensitivity of 50% for *S. aureus*; 20-30% for other bacteria

• 1500 acetabular cup revisions for “aseptic loosening” found to be actual infections by FISH
What’s new and related to Biofilm

• 26 revisions of total joint revisions
• IBIS T5000 (DoD) followed by deep sequencing and FISH
  – 8 *S. aureus* (vs only 4 by culture)
  – 7 CoNS (vs only 1 by culture)
  – 1 strep (1 strep by culture)
  – Remaining 10 entero, providenciae, etc (0 by cx)
  – 6 by culture / 26 by IBIS
  – Plex ID (Abbott)
Take Home Points

• Make up 80% of infections treated by physicians in developed countries
• Complicated communities w/ signalling
• Resistant to host defenses and antibiotics
• Will not grow – unless releasing planktonic
• Treatment is removal
• New signalling interrupters / dispersants show promise – not for CF patients due to possibility of overwhelming lung
Bacteria in biofilms tend to be more difficult to culture and more resistant to control strategies (antibiotics and biocides) and host defenses than when grown planktonically in the laboratory.

Their resilience has been related to physiology and protection by the EPS slime matrix that they produce.

These phenomena may explain seemingly conflicting features of the disease when signs and symptoms are otherwise consistent with infection.

• Chronic in Nature
• Culture Negative
• Poor Response to Antibiotics
• Potential for Metastasis
Closer to the Bone:
Hard Tissue Infection-Osteo

• How common in DM? 20% of all patients w/ foot infections- over 60% of those w/ severe ones requiring hospitalization

• However – even if wound looks good can still have underlying bone infection

• Associated w recurrence / poor wound healing

• Increases risk of amputation 5-8x (some studies – 20x more likely)
• According to a survey up to ¼ respondents accept/expect a failure rate of 25%

• “Bone of Contention” editorial highlighting controversy and lack of clarity by Elie Berbari
History & Physical Findings

• Prolonged wound duration or recurrent wound; previous episode involving same bone
• Discharge of bony fragments, Over bony prominence, visible bone,
• Deep (>3mm) or large >2sq. Cm

• Positive probe to bone test (high IO variability – highly user dependent ) use metal not swab tip or plastic; PPV = 89% - but 5 more studies suggest not so high and doesn’t not obviate need for imaging
• Also depends on prevalence or pretest probability – if high ( limb threatening infections) then good
Diagnosing Osteo...

• Which is best ESR, CRP Procalcitonin WBC?

• ESR >70 is associated w/ osteo (CRP procalcitonin better for soft tissue)

• Indium 111 WBC scan better than bone scan b/c the latter too nonspecific – some experts don’t even use

• MRI is best Pos. LR is 4 or higher
Looking at the evidence base for diagnosing osteomyelitis

- 2 systematic reviews

- First only looked at positive bone cults – there were 9 studies *Clin Infect Dis*
  - Probe to bone or exposed bone OR* >50
  - MRI 25 > WBC Scan > Bone scan

- 2\textsuperscript{nd} published in JAMA; 21 studies
  - PTB pos. LR 6, neg. LR 3; ESR >70 had OR* of 11;
  - Ulcer > 2 cm had OR* 7; + MRI OR* of 3.8

* odds ratio
• Take home: if patient is very likely or very unlikely to have osteo none of these tests move you much along the decision spectrum more than tossing a coin

• So most useful in middle ground – like GXT

• New imaging modalities
  – SPECT CT- radionuclide CT scan – best of CT and nuclear medicine
  – PET MRI
International Working Group of Diabetic Foot

• Definite:
  – Positive bone bx PLUS positive histology
  – If saw pus in bone at time of surgery
  – If automatically detached bone frag in ulcer
  – Interosseous abscess on MRI

• Probable:
  – Visible cancellous bone
  – Positive culture OR histology but not both
  – Suggestive MRI
• Possible:
  – Any combo of ESR, history and physical and not a probable or definite
  – If have 1 definite chancers are greater than 90% and can just treat

• So-
  – If 2 probable or 1 probable plus 2 possible chance is 50-90% so can consider treating but consider further diagnostics
  – Only 2 possible chance is 10-50% so need more tests
Gold standard for osteo?

• Best test is biopsy of bone- sent for CX AND histo path
• Difficult to convince people to do – fear of complications
• But safe- 2000 reports in the lit only one fracture – sacral biopsy
• No reported complications in the diabetic foot
• Possible outcomes:
  – False positive if go through dirty or contaminated skin or wound
  – False negative if miss area
• Use fluoro / IR suite
Evidence for surface swabs?

• One study using a positive bone culture as gold standard

• Compared swab culture of a cleaned wound to bone culture in patients w/ proven osteo

• Concordance poor

• Swab missed most of Staph aureus recovered in the bone, and yielded gram negatives which were not recovered in the bone so get false positives w/ gram negatives and false negatives w/ staph aureus, so using swab results to guide osteo therapy is risky business
What about negative bone cx?
Does Bone cx improve outcome?

• In the biggest/best study (340 French patients) if had a negative culture and followed for 2 years (n=41) 75% of the time the patient healed and didn’t develop osteo. But 25 % ??

• Does doing a bone cx result in better outcomes – 50 evaluated, 22 selected on bone, 28 selected on basis of swab- median duration of TX 3 months- remission rate – 83% in bone cx directed vs 50% in those who had swab directed therapy

• Retrospective w/ confounders and there were more patient in cx group and more may have had rifampin
Upcoming Systematic Review in Clin Infect Dis for chronic osteo in adults:

• Oral agents w/ high Bio avail – ok (may need higher dose) acceptable alternative to parenteral

• Adding rifampin may improve cure rates

• Surgical resection of bone increases cure rates

• Not “cured” unless has no recurrence for a more than a year (late recurrent are common)
Diabetic Osteo Foot Infections: Guidelines from Working Group

• ‘To bead or not to bead’? Pros and cons paper out soon
  – no prospective studies proving value, increasing resistance may further limit resistance
• No abx agent can be recommended empiric regimens should include anti staph agent and MRSA if high prevalence
• Non data supports HBO, GCSF, vacs or larvae
• But larvae deserve more respect in my opinion
How Long Is Long Enough?

- When to stop - harder decision than starting
- Very little evidence
- Now shorter course indications and biomarkers
  - CAP quinolones 5d
  - AECB 5d
  - UTI- 3-5d; CAP5d; HAP 8d – well supported
    - Unless Acinetobacter or Pseudomonas
  - Procalcitonin driven algorithm vs. standard TX
    - No difference in 30 day mortality
    - But sig. less Adverse Events and less costly b/c less abx use
Working Group Recommendations for osteomyelitis

- 2-5 days if cut all bone and tissue out
- Residual soft tissue not involving bone: 1-3 weeks
- Residual infected but viable bone: 4-6 weeks
- Residual dead bone: ≥12 weeks or more
Digression: What about *Staphylococcus aureus* bacteremias?

- Data unclear
- Interestingly vanco MIC is independent predictor of complications for MRSA and MSSA - didn’t matter nor did treatment
- 1.5
- Removable focus, no comorbidities, no other joints or devices, etc etc etc ... now add vanc mic 1.5 – and you’ll be a hero
Why Limit Duration?

- The Crisis of antibiotic resistance
- Greatest threat to global public health
- Bad Bugs, No Drugs, No ESKAPE
- Almost no drug companies developing new compounds
- None in late stage trails
- Resistance develops rapidly (mobile genetic elements)
Why Limit Duration?

• Stop irritating them is likely best way to limit future resistance
  – Vs blast them vs. fool them
  – But not a linear / direct relationship

• Some say narrowing down is a misnomer
  – Imipenem to ampicilllin
  – Imi no enterococcus; amp big effect on gut bugs
Drug Dosing – Optimizing Effectiveness

• What is more important for clinical impact? PK-PD or MIC?

• MIC > PK-PD, but as MIC goes up, PK-PD gets more important

• TAR drops dramatically for cefepime and imipenem as MIC approaches breakpoint
Boosting the Efficacy of Carbapenems by High Dose and Prolonged Infusion

- A 500-mg dose of doripenem 4h infusion every 8h would be expected to be effective for bacilli with MICs to doripenem of up to 4 μg/ml with a T>MIC 35%.

- A 1-g dose of doripenem 4h infusion would provide adequate coverage for pathogens with MIC as high as 8μg/ml with a T>MIC 52.5%.

- A 2g dose of doripenem 4h infusion would be adequate even for pathogens with MIC of 16μg/ml obtaining a T>MIC 52.5%.

Samtani MN, et al. AAC 2010;54:2360
Bulik CC, Nicolau DP. AAC 2010;54:4112
Pharmacodynamic Attainment of Piperacillin/Tazobactam 4.5g q6h (0.5)

5000 patient Monte Carlo simulation

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<td>11.3</td>
<td>20.4</td>
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<td>25th</td>
<td>34</td>
<td>7.5</td>
<td>15.5</td>
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<td>75th</td>
<td>51</td>
<td>15.8</td>
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Piperacillin/tazobactam Failures versus Bacteremic Pseudomonas aeruginosa

Figure 1: Thirty-day mortality rate for patients with bacteremia due to Pseudomonas aeruginosa, according to piperacillin-tazobactam MIC.
Drug Dosing in Difficult Situation

• Take home – more aggressive maximal doses (MAMD)
• Sicker patients = MAMD
• Nursing home = MDRO = MAMD
• All because of risk of underdosing
• What about renal replacement? ....
Drug Dosing in Difficult Situation

- CRRT- big black box- two rules of thumb not so good
  - Just dose like they had a CrCl of 25-50
  - Look at total effluent from machine – that is surrogate CrCl
  - But big risk of underdosing
  - Even w/ manufactures recommended doses – sometimes need double MRD or full dose
  - For soft tissue and lung AG no good b/c of poor penetrations (hydrophilic)

- If you don’t need, don’t use – especially in elderly or if there is a narrow therapeutic window
Thank you

• Questions?
• Consider isolate submission to:
  • Multidrug-resistant organism Repository and Surveillance Network
  • Fatal infections, pan-resistant, outbreaks,
  • emil.lesho@us.army.mil
Case Presentation

- 75 years old ♂ with aspiration pneumonia, resident of Health-Care Facility
- On admission: $PO_2$ 45, $PCO_2$ 67 → transfer to ICU → mechanical ventilation
- Started Pip/Tazo. Sputum culture on day 3: *P. aeruginosa* sensitive to all except Caz and Cipro → slow improvement
- **On day 12:** Afebrile, weaning efforts
- **On day 16:** The patient deteriorates, multiple pulmonary shadows (VAP): new fever (39.2°C)
- Treatment changed empirically to colistin plus meropenem
Case Presentation

- **On day 19:** Bronchial secretions cultures:

  XDR *K. pneumoniae* with Colistin MIC 32, Tigecycline 4, Meropenem 8, Fosfomycin 32, Gentamicin 4µg/ml

  - Would you discontinue colistin?
  - Would you trust monotherapy with tigecycline?
  - Would you add fosfomycin?
  - Would you prefer colistin+tigecycline?
  - Would you add gentamicin?
  - Would you discontinue meropenem?
1. **Pandrug Resistant (PDR):**
   To all classes of antibiotics, since in the Greek language the prefix “pan-” means “all” or “whole”

2. **Extensively Drug Resistant (XDR):**
   To all classes of antibiotics except 1 or 2 (usually colistin ± tigecycline)

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International Incidence of Mortality:
Infections Caused by KPC and MBL Producing Bacteria

22% to 75%

Risk factors of death:
- R to carbapenems
- Older age
- Severity of underlying disease
- Delay in initiating appropriate empirical therapy

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Folagas ME, Karageorgopoulos DE. CID 2008;46:1121
Magiorakos AP, et al. CMI 2011

HOW TO TREAT?
The Last Resort Antibiotic in the Era of XDR Gram-Negative Microorganisms

- **Pseudomonas aeruginosa** (IMP, MBL, KPC)
  - Colistin
  - Fosfomycin

- **Klebsiella pneumoniae** (ESBL, MBL, KPC, NDM-1)
  - Colistin
  - Tigecycline
  - Fosfomycin

- **Acinetobacter baumannii** (AmpC, ESBL, MBL, OXA-48)
  - Colistin
  - Tigecycline

To Treat or Not to Treat with a Carbapenem?
Literature Review Outcomes (until July 2011) of 294° Patients with Carbapenemase Producing Serious *K. pneumoniae* Infections According to Antimicrobial Regimens

- **Carbapenem** (MIC ≤4μg/ml)** in combination with other active*** antibiotics
- Other combinations of two active*** antibiotics without a Carbapenem
- Carbapenem** monotherapy (MIC≤4μg/ml)
- One active*** antibiotic monotherapy (without a Carbapenem)
- No active antibiotic

*KPC and VIM, few IMP
**Mostly imipenem or meropenem
***Colistin, tigecycline, aminoglycoside

*From 294 infections: 79% bacteremias, 15% HAP+VAP

Daikos GL. Manuscript in Preparation
Carbapenemase-producing *Klebsiella pneumoniae*: To Treat or Not to Treat with a Carbapenem?

- Carbapenem monotherapy (imipenem, meropenem, doripenem) for strains with MIC >4μg/ml should be prohibited, whereas for strains with low MICs (≤4μg/ml) better to be avoided.

- Carbapenems may be a reasonable treatment option against carbapenemase producing *K. pneumoniae*, provided that:
  1. The carbapenem MIC for the infecting organism is ≤4mg/l.
  2. Carbapenem is given in combination with another active compound, i.e. colistin, tigecycline, aminoglycosides.
  3. Carbapenem is given in high dose and prolonged infusions (3-4 hours)

*Daikos GI, Markogiannis A. CMI 2011;17:1135*
Boosting the Efficacy of Carbapenems by High Dose and Prolonged Infusion

- A 500-mg dose of doripenem 4h infusion every 8h would be expected to be effective for bacilli with MICs to doripenem of up to 4 µg/ml with a T>MIC 35%.

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Figure 1: Thirty-day mortality rate for patients with bacteremia due to Pseudomonas aeruginosa, according to piperacillin-tazobactam MIC.
Cefepime Pharmacodynamics

Probability of achieving 50% T>MIC for VAP patients (CrCl: 50ml/min – 120ml/min)

Characteristics and Treatment Outcome with Colistin for Infections Due to MDR and XDR Gram-negative Bacteria

**Literature Review: 1999-2007**

- In 13 studies with 453 patients (380 ICU)
  - Clinical Cure Rate: 52%-73%
  - Mortality Rate: 20%-62%
  - Nephrotoxicity: 8%-37%
- However, all studies share similar methodological problems, i.e. non-comparative, retrospective trials, with simultaneous use of imipenem in 70%-100% of patients and dose variability.
The Few Recent Comparative Studies with Colistin as Monotherapy Against XDR Gram-negatives

Kallel H, et al. Intens Care Med 2007;33:1162

- Retrospective study
- 60 vs 60 pts with VAP caused by XDR P. aeruginosa or A. baumannii (versus imipenem)
- Successful result: 75% vs 72%
- Infection related mortality: 16.7% vs 11.6% (p=NS)


- Prospective, non randomized, cohort study
- 200pts vs 295pts (versus active antibiotic) mostly with VAP and bacteremia
- K. pneumoniae KPC(+) in 52% vs 27%
- 30day mortality: 39% vs 29% (p=0.018)
- Higher rates of septic shock, secondary infections, Proteus and Serratia spp infections and prolonged hospital stay in Colistin group
Colistin: Monotherapy versus Combination Therapy in 258 Greek ICU Patients Against *P. aeruginosa* and *A. baumannii* Infections

![Bar chart showing percentage of cure and deterioration for different treatments](Falagas, et al. Int J Antimicrob Agents 2010)
In Vitro Evaluation of Combinations

Bactericidal activity was achieved in 90% of all bacteria assayed using combinations of polymyxin B, doripenem, and rifampin.

Colistin MICs determine the in vitro result of the combination with imipenem against metallo-β-lactamase-producing (VIM1) Klebsiella pneumoniae.

However...

Irrespective of Imipenem MIC (range 1->32μg/ml) the combination was:

1. Synergistic (50%) against colistin-susceptible strains (Colistin MICs 0.2 – 4 μg/ml)

2. Antagonistic against 55.6% of non-colistin-susceptible strains (colistin MICs 16-128 μg/ml)

M. Souli, H. Giamarello. AAC 2009; 53: 2133
Retrospective Analysis of Colistin Therapy of 258 MDR and XDR Gram-negative Infections:

Mortality Analysis

1. Multivariate analysis: Higher daily colistin dose was associated with increased probability of survival (p=0.009)
   - 3mil iu/daily: 38.6%
   - 6mil iu/daily: 27.8%
   - 9mil iu/daily: 21.7%

2. Mortality rate in univariate analysis:

Population Pharmacokinetic Analysis of Colistin after Intravenous Administration in Critically Ill Patients with Infections Caused by Gram-Negative Bacteria

- Slower formation of Colistin by CMS than previously described
- Longer Colistin half-life: 14.4h
- Sub-therapeutic concentrations (0.6μg/ml), after 3 mil iu every 8 hours, during the first day, that may lead to:
  - Treatment failures
  - Emergence of resistance

Usual dose 3 mil iu x3
1mg of Colistin = 12,500 iu
The administration of a loading dose of 6 MU CMS resulted in colistin plasma concentrations above 1mg/L within 4 hours in the majority of the patients.

**Suggested Colistin Dosing for Various Patients Category**


<table>
<thead>
<tr>
<th>Loading dose</th>
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<tbody>
<tr>
<td><strong>Targeting peak blood level of 2μg/ml in all patient category</strong></td>
</tr>
<tr>
<td>Body weight divided by 7.5</td>
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<tr>
<td>(maximum permitted dose 10 mil iu)</td>
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<tr>
<th>Maintenance dose</th>
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<tr>
<td><strong>Normal renal function</strong></td>
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<tr>
<td>(Clcr divided by 10) + 2 given in 2-3 doses</td>
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<tr>
<td>S.O.S. The 1st dose should be given 24h post loading dose</td>
</tr>
<tr>
<td><strong>In Hemodialysis</strong></td>
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<tr>
<td>2 mil iu in two daily doses</td>
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<tr>
<td>S.O.S. On the day of hemodialysis 30% of the daily dose should be given post hemodialysis</td>
</tr>
<tr>
<td><strong>In continuous hemofiltration</strong></td>
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<tr>
<td>12 mil iu in two or three daily doses</td>
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* Ideal or real body weight in Kg (choose the least)
The Efficacy of Other Routes of Administration of Colistin

Intrathecally/Intraventricularly for XDR A. baumannii meningitis

- 40 pts: 125,000-500,000 iu daily
- Cure rate: 84%-93%
- S.O.S. Chemical meningitis in 15%-28%

As adjunctive Inhalation Therapy in VAP?

- 500,000-1,000,000 iu 8hourly
- 78 vs 43pts: Cure rate 80% vs 61%
  - Korbilla IP, et al. CMI 2010;16:1230
- 43 vs 43pts: Cure rate 60% vs 75% (p=0.1)
- Cure rate: No difference in the therapy of VAP
  - Kofteridis DP, et al. CID 2010;51:1238
- S.O.S.: Use a mesh or plate vibrating nebulizer
4 Eras of colistin usage

1st = 1950-1970 initial
2nd = 1997-2005 resurgence ...back to the future
3rd = 2010-2011 period of rational use ....PK-PD
Colistin-resistant isolates of *Klebsiella pneumoniae* emerging in intensive care unit patients: first report of a multiclonal cluster

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Unfortunately Nowadays Emergency of KPC(+) *Klebsiella pneumoniae* Resistant to Colistin is Expanding from S. Korea, Hungary, Sicily, even from Detroit

Suh JY, et al. AAC 2011; 54:560
Toth A, et al. EJCMD 2010; 29:765
Mezzatesta ML, et al. CMI 2011; 17:1444
Marchain D, et al. AAC 2011; 55:593
Colonization and Infection by Colistin Resistant Gram Negative Bacteria in a Cohort of Critically Ill Patients in Greece

Among 150 ICU patients:
- 52% were colonized with Colistin-R Gram-negatives:
  - 20% with *K. pneumoniae* and 34% by CR *Proteus* spp. and *Serratia* spp.
- 25% developed infections
- All cause mortality: 75%
- The main risk factor was duration of colistin pretherapy (>20d)

Plachouras D, Giamarelou H, et al. CMI 2011 accepted
To Rescue Colistin and while Awaiting Culture Results... When to Treat Empirically with Colistin?

Severe nosocomial sepsis/or septic shock in settings with XDR prevalence.

In serious nosocomial infections, whenever risk factors for XDR Gram-negatives are present, i.e.:
- Preceded VAP episodes
- Preceded therapy with a carbapenem or superinfection while treated with a carbapenem
- Preceded ICU hospitalization
- Known colonization with XDR

After Culture Results to Rescue Colistin: Do not Forget De-escalation!