

Treating Common Infections in Diabetics

Jonathan Vilasier Iralu, MD FACP

Indian Health Service Chief Clinical Consultant for Infectious Diseases

Case Presentation 1

A 35-year-old woman with a history of diabetes on insulin has had a cough for 3 days. On physical exam she has a fever of 102.3, pulse 124, respiration 26 and BP 90/46. She appears toxic and has labored breathing. The lung exam is notable for left base bronchial breath sounds and egophony. Lab exam is notable for BUN 22, Creatinine 0.8, WBC 15K. CXR confirms a LLL pneumonia with a small non-layering effusion



Questions 1

- What is the impact of diabetes on this patient?
- Where should the patient go?
 - Home
 - Medical Ward
 - ICU
- What antibiotics should be started?
- What should be avoided?
- What can be done to prevent pneumonia?

Impact of Diabetes on Pneumonia

- Kornum et al Diabetes Care 30: 2251-2257, 2007
 - Population based cohort control study
 - 29,900 patients with pneumonia in Northern Denmark
 - 9.8% of the patients had Diabetes mellitus type 2
 - Mortality was 19.9% vs 15.1% for diabetics versus other patients at 30 days and 27% vs 21% at 90 days
 - Diabetes was not a predictor of pulmonary complications of bacteremia
 - **High blood glucose was a predictor of death**

<https://pubmed.ncbi.nlm.nih.gov/17595354/>

Evaluation: 2019 ATS/IDSA Guidelines

- **Testing**

- Sputum culture for those with severe disease/Rx for MRSA/Pseudomonas
- Blood culture for those with severe disease/Rx for MRSA/Pseudomonas
- **Test for flu when flu is circulating (*don't forget COVID-19!*)**
- **Procalcitonin not recommended**
- Follow-up CXR not recommended

<https://www.atsjournals.org/doi/full/10.1164/rccm.201908-1581ST>

2019 ATS/IDSA Guidelines: Definition Severe CAP: 1 Major or 3 Minor

- Minor Criteria

- RR > 30
- PaO₂/FiO₂ < 250
- Multilobar infiltrates
- Confusion/disorientation
- Bun > 20
- WBC < 4K
- Platelets > 100
- Core Temperature < 36
- Hypotension requiring fluids

- Major Criteria

- Septic Shock needing pressors
- Respiratory failure needing ventilator

<https://www.atsjournals.org/doi/full/10.1164/rccm.201908-1581ST>

Triage of the Pneumonia patient

- CURB-65 from the BTS

- Confusion
- BUN > 20
- RR > 30
- SBP < 90 or DBP < 60
- Age >65

- Interpretation:

- 0-1 Outpatient
- 2-3 Inpatient
- 4-5 ICU

<https://www.mdcalc.com/curb-65-score-pneumonia-severity>

- PSI/PORT Score preferred by ATS

- SNF resident
- Cancer/CHF/CKD/Liver Disease/Stroke
- Altered mentation
- RR > 30
- BP < 90
- T < 35 or >39.9 C
- HR > 125
- Labs: oH < 7.35, Bun > 30, Na ,130, Glucose> 250, HCT ,30%, PaO₂< 60
- Pleural Effusion

<https://www.mdcalc.com/psi-port-score-pneumonia-severity-index-cap>

2019 ATS/IDSA Guidelines: Outpatient Pneumonia

- No Comorbidities or risk factors for MRSA/Pseudomonas (prior infection, IVAbx < 90 days)
 - Amoxicillin
 - Doxycycline
 - Azithromycin (if local resistance is < 25%). → Most of the US is >30%!
- Comorbidities including Diabetes mellitus:
 - Amoxicillin-clavulanate (or advanced generation cephalosporin) plus a macrolide or doxycycline
 - Levofloxacin 750 mg po daily x 5 days
 - Use this drug only if allergic to the regimens above
 - Use with extreme caution in pneumonia Rx:
 - C difficile collateral damage.
 - This drug masks tuberculosis.
 - This drug causes dysglycemia.

Empiric Treatment of Community Acquired Pneumonia with Fluoroquinolones, and Delays in the Treatment of Tuberculosis

- Dooley et al (CID 2002): retrospective analysis of 33 pts with TB
 - 48% received prior quinolone therapy for pneumonia
 - Patients who received quinolones started 1st TB meds at day 21
 - Patients who did not started 1st TB meds at day 5
- Chen et al (Int J of ID 2011): meta-analysis of 9 eligible studies
 - Quinolone Rx delayed TB Rx by **19 days**
 - The **RR** of quinolone resistant TB developing was **2.7**

2019 ATS/IDSA Guidelines:

- Non-severe Inpatient pneumonia
 - Ceftriaxone 1 gm IV daily plus Azithromycin 500 mg IV daily
 - Levofloxacin monotherapy if allergic to beta-lactams
- Cautions/Substitutions
 - Use caution in using macrolides in patients with heart disease
 - Use caution in using macrolides and quinolones in patients with QTc prolongation
 - Doxycycline 100 mg IV q 12h can be substituted for Azithro or Levo

<https://www.atsjournals.org/doi/full/10.1164/rccm.201908-1581ST>

2019 ATS/IDSA Guidelines: Severe Inpatient Pneumonia

- Severe Inpatient Pneumonia
 - Ceftriaxone 1 gm IV daily plus Azithromycin 500 mg IV daily
 - Ceftriaxone 1 gm IV daily plus Levofloxacin 750 mg IV daily)
- Prior MRSA: Add vancomycin or Linezolid to the above
- Prior Pseudomonas: Substitute in Pip-Tazo, Cefepime, Meropenem for the Ceftriaxone

<https://www.atsjournals.org/doi/full/10.1164/rccm.201908-1581ST>

Hospital Acquired Pneumonia

- Treatment depends on:
 - Local drug resistance prevalence (MRSA >20%), Pseudomonas/GNRs > 10%)
 - Prior IV antibiotics within 90 days
 - High risk of mortality (Intubation or shock)
- If no risk of MRSA, ,(No IV Abx Hx, not high risk), treat with Pip-Tazo, Cefepime, Levofloxacin, Meropenem
- If at risk for MRSA, give Vancomycin or Linezolid as well
- If at risk for Pseudomonas/GNRs, give a beta-lactam plus a quinolone

<https://academic.oup.com/cid/article/63/5/e61/2237650>

Other special situations...

- Aspiration Pneumonia options:
 - Ampicillin Sulbactam 3 gm IV q 6h
 - Piperacillin Tazobactam 3.75 gm IV q 6h
 - Clindamycin 600 gm IV q 6h
- Influenza
 - Oseltamivir 75 mg po bid for 5 days
- Hantavirus
 - Transfer patient to tertiary care center for ECMO
- Tuberculosis
 - Avoid quinolones
 - Airborne Isolate if upper lobe, miliary, immunocompromised, unexplained effusion
 - Consult ID early

How Long to Treat

- Community Acquired Pneumonia
 - 5-7 days
- Hospital Acquired Pneumonia
 - 7-8 days
 - Chastre et al, JAMA, 2003: 8 vs 15 days of therapy
 - Mortality 18.8% vs 17.2
 - Recurrence 29.9% vs 26%
- Duration of therapy not modified for diabetes

Vaccination

- Influenza:
 - All patients > 6 months of age

Pneumococcal Vaccination: New ACIP Guidance 2022

- Pneumococcal Conjugate Vaccine:
 - PCV-20 x 1 or PCV 15 followed by PPSV in 6-12 months
 - **All patients 65 and older**
 - **Patients aged 19-64 with chronic medical conditions:**
 - **DM**
 - Alcohol Use Disorder
 - CHF, Chronic liver disease, COPD, emphysema, asthma, CKD, nephrotic syndrome
 - CSF leak/Cochlear implants or asplenia
 - Cigarette smoking
 - Sickle Cell anemia
 - HIV, Congenital or acquired immunodeficiency, Leukemia/Lymphoma/Myeloma, Generalized malignancy, Solid Organ Transplant, iatrogenic immuno-suppression (steroids, XRT, etc)

New Review in Annals of Internal Medicine

Annals of Internal Medicine®

In the Clinic®

Community-Acquired Pneumonia

Community-acquired pneumonia (CAP) can vary from a mild outpatient illness to a more severe disease requiring hospital admission and, at times, intensive care. CAP is the eighth leading cause of death, along with influenza, and is the leading cause of death from infectious diseases in persons in the United States older than 65 years. The key management decisions related to CAP are recognition and treatment in a timely and effective manner, defining the appropriate site of care (home, hospital, or intensive care unit [ICU]), and ensuring



<https://www.acpjournals.org/doi/pdf/10.7326/AITC201510060>

Tuberculosis and DM

- DM increases the risk of reactivation of Latent TB infection three-fold
- The prevalence of TB infection is as high as 30% in some IHS Areas
- TB death rates for American Indian patients in the US are up to **15-fold** higher than for white patients
 - (Reilley et al, Am J Public Health. 2014 Jun;104 Suppl 3:S453-9)
- **Latent TB infection can now be treated with just 12 weekly doses of Isoniazid and Rifapentine. (3HP)**

Photograph 1



Case Presentation 2

A 34-year-old man with DM type 2 is seen in the Urgent care clinic with a red, hot swollen left leg. He abraded his ankle 5 days ago has a 1 cm purulent ulcer over the anterior surface with purulent drainage. He was seen elsewhere yesterday and was placed on Cephalexin 500 mg po qid but today says his leg is worse.



Cellulitis

- How does diabetes impact this patient?
- Is inpatient treatment needed?
- What is the best antibiotic for this patient?
- Are there special considerations?

Diabetes and Soft Tissue Infections

- Pathogenesis:
 - C4 Complement levels are lower in DM
 - Mononuclear cells secrete less IL-1 in diabetics
 - Hyperglycemia causes decreased polymorphonuclear leukocyte mobilization, chemotaxis, phagocytosis, and transmigration across the endothelium
 - CD4 lymphocyte proliferation is not impaired if the HbA1c is < 8%
 - Glycation of immunoglobulin increases with increasing HbA1c

Casqueiro et al, Indian J Endocrinol Metab. 2012 Mar; 16(supp 1): S27-36

Outpatient vs Inpatient Rx for Cellulitis

- Consider admission:
 - Failure to respond to oral antibiotics
 - Infection involving the hand and face
 - Systemic Inflammatory Response symptoms: high fever, hypotension
 - **Findings consistent with a severe soft tissue infection**
 - SIRS
 - Blister formation
 - Necrosis
 - Pain out of proportion to appearance of skin

<https://academic.oup.com/cid/article/59/2/e10/2895845>

Outpatient Cellulitis

- No draining wound
 - Cephalexin 500 mg po qid for most cases
 - Use Clindamycin 300 mg po TID if PCN/cephalosporin allergic
- Draining Wound = MRSA!
 - Trimethoprim Sulfa DS 1-2 po bid or Doxycycline 100 mg po bid
- Draining Wound but Strep suspected
 - Trimethoprim Sulfa DS 1-2 po bid plus Keflex 500 mg po qid
 - Trimethoprim Sulfa DS 1-2 po bid plus Clindamycin 300 mg po qid

<https://academic.oup.com/cid/article/59/2/e10/2895845>

Inpatient Cellulitis

- **Moderate infection** with *no drainage*:
 - Cefazolin, Ceftriaxone, Clindamycin, or PCN
- **Severe Infection** with *no drainage*:
 - ***Consult surgery immediately***
 - Vancomycin **plus** Piperacillin-Tazobactam
- **Specific Therapy**
 - Gp A Streptococcus: High dose PCN plus High dose Clindamycin
 - Clostridium species: High dose PCN plus High dose Clindamycin
 - Vibrio vulnificus: Doxycycline plus Ceftazidime
 - Aeromonas: Docycycline plus Cipro
 - Polymicrobial: Vancomycin plus Piperacillin-Tazobactam

<https://academic.oup.com/cid/article/59/2/e10/2895845>

Inpatient Cellulitis: Draining Wound, Part 1

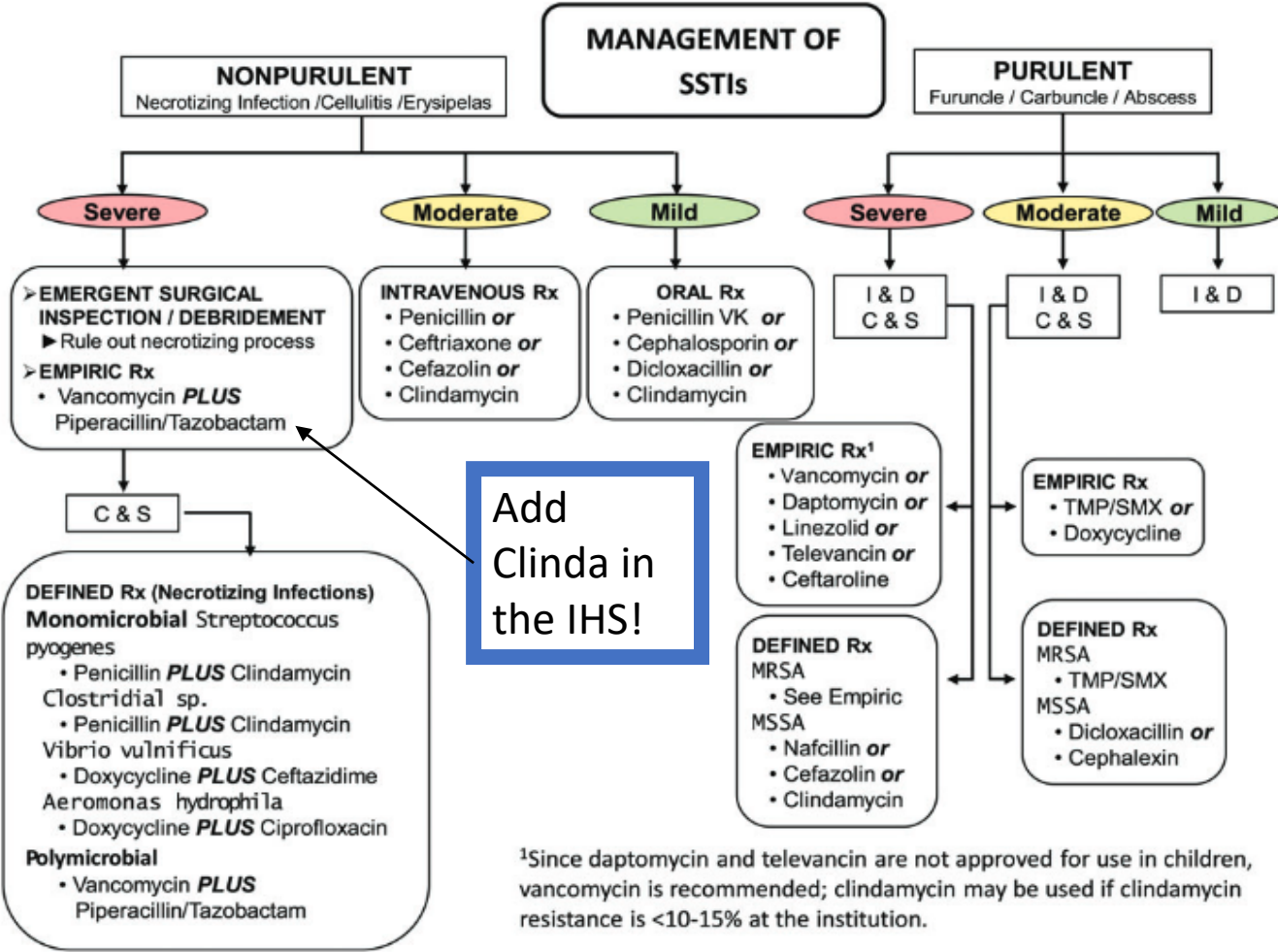
- Inpatient cellulitis with draining wound (*Use PCR if available*):
 - Vancomycin 15, mg/kg IV q 8-12h
 - Linzeolid 600 mg IV q 12h (better in CKD)
 - Daptomycin 4 mg/kg IV daily (beware CPK incr, eosinophilic pneumonia)
- If MRSA, continue one of the above
- If MSSA, switch to Cefazolin, Nafcillin or Clindamycin

<https://academic.oup.com/cid/article/59/2/e10/2895845>

Inpatient Cellulitis: Draining Wound, Part 2

- Consider adding Clindamycin if there is an abscess
- Wargo et al, Clin Infect Dis, October 1, 2015
 - Retrospective review of 269 bacterial skin infection in 941 bed in northern Alabama
 - Vancomycin **vs** vancomycin plus clindamycin
 - Addition of clindamycin led to improved outcomes
 - **Length of stay was 18.2 % shorter** with addition of clindamycin [**OR 0.81**]
 - **Readmission rate** at 90 days was 5.3% with clindamycin, 15.3% without [**OR 3.2**]

Management of SSTIs Graphic



Diabetic Foot Infection Diagnosis - 2012 IDSA Guidelines

- Diabetic foot ulcers
 - Don't culture if not infected!
 - Culture wound before starting antibiotics
 - Swabs are inferior
 - Preferred culture is deep tissue biopsy after wound cleansing and debridement
- Osteomyelitis
 - Probe to bone test if there is an open wound
 - Plain films are low sensitivity and specificity but recommended
 - **MRI is the best test** to rule out osteomyelitis
 - Debrided bone biopsy is most definitive.
 - Consider needle biopsy if there is uncertainty

<https://academic.oup.com/cid/article/54/12/e132/455959>

IDSA DFI Severity Rating

- Mild
 - Local infection of skin **0.5-2cm** around ulcer
 - Rule out noninfectious causes (gout, Charcot joint, DVT, etc)
- Moderate
 - Local Infection: Inflammation extends **>2cm** around the ulcer
 - No SIRS
- Severe
 - Local Infection plus SIRS
 - T>38 or <36
 - HR >90
 - RR>20 or PaCO<32
 - 'WBC >12K or < 4K or bands >10%

<https://academic.oup.com/cid/article/54/12/e132/455959>

Who to admit...

- Admit all Severe
- Admit moderate if there is a complicating feature
 - Peripheral arterial disease
 - Poor home support
 - Non-adherent patient

<https://academic.oup.com/cid/article/54/12/e132/455959>

Diabetic Foot Infection Treatment Part 1

- Mild Outpatient case (Focus on aerobic Gm Positive Cocci)
 - Amox-Clavulanate 850 mg po bid (add TMP/SMZ if MRSA is likely)
 - Clindamycin 300 mg po tid plus Cipro 500 mg po bid if PCN allergic
 - Consider Keflex for mild cases with no prior antibiotic exposure

Diabetic Foot Infection Treatment Part 2

- Inpatient case or OPAT
 - Piperacillin-Tazobactam 3.375 gm IV q 6h if severe or pseudomonas suspected
 - Ertapenem 1 gm IV daily (convenient for OPAT)
 - Consider adding empiric vancomycin or linezolid **if severe** or already **MRSA (+)**
- Avoid automatic “VANCO-SIN” unless it’s a necrotizing infection

Diabetic Foot Infections

- Mild infection
 - Treat **1-2 weeks**
- Moderate to Severe
 - Treat **2-3 weeks**
- Osteomyelitis
 - If all infected bone has been resected
 - Treat for **14-21 days** (IV plus PO)
 - Treat **2-5 days** after radical resection (BKA)
 - If residual osteomyelitis is present treat for **6 weeks with IV therapy**

Hand Infections

- Extremely mild, very early onset, outpatient case (*very very rare*)
 - Amoxicillin-Clavulanate 875 mg po bid
- Inpatient case (*the majority of hand infections*)
 - Ampicillin-Sulbactam 3 gm IV q 6h
 - Add vancomycin if MRSA is suspected (prior infection, severe disease)
- Special considerations
 - **Most hand infections should be admitted to the hospital**
 - Surgical consultation for urgent debridement is the key to success

Necrotizing Fasciitis

- Diagnosis
 - Severe pain
 - SIRS
 - Blue black discoloration, bullae
- Empiric Therapy
 - Vancomycin or Linezolid plus Piperacillin-Tazobacam or Meropenem **plus Clindamycin**
 - Urgent Surgical debridement
 - Use High dose PCN **plus** Clindamycin if Group A Strep isolated
 - *Consult ID, please!*

Group A Streptococcal Infection in American Indians

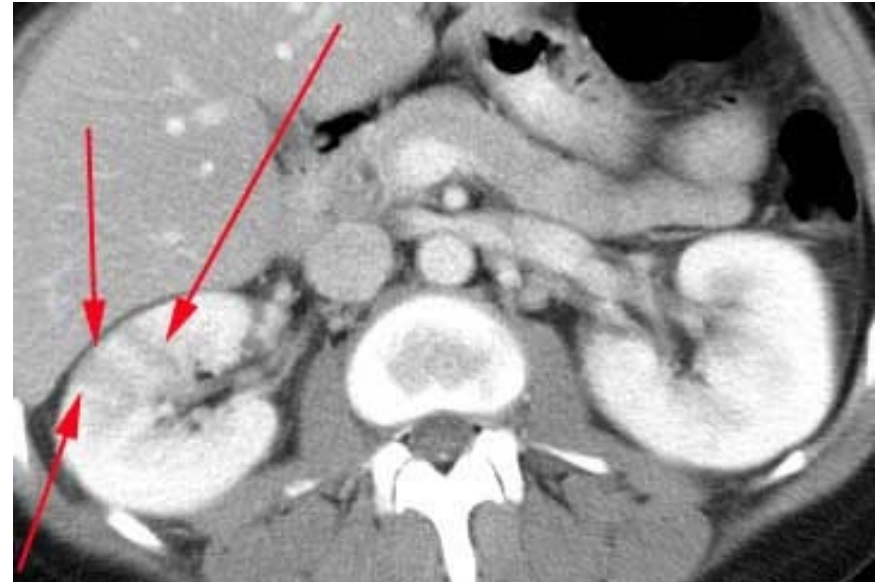
- Recent outbreak of Community Acquired invasive Gp A Strep
 - **Three-fold increase 2012-2013 in one Arizona hospital**
 - 11 cases diagnosed
 - All were AI
 - Nine (82%) had open wounds/abrasions
 - Nine (82%) had underlying obesity, DM, CKD, heart disease or alcoholism
 - 2 had bacteremia
 - **4 had Necrotizing fasciitis**
 - Prophylaxis was given to contacts
- Harris A, Yazzie D et al. Community Acquired Invasive GAS Disease among Native Americans. Emerging Infect Dis 2015

Photograph 2



Case Presentation 3

A 65-year-old female with Diabetes Mellitus type 2 and CKD II presents to the clinic with dysuria and urinary frequency. She is treated with cephalexin and is discharged home. Three days later she presents with a fever, left flank pain and vomiting. She has a moderately ill appearance and her blood pressure is 80 systolic. She is admitted to the ICU and her blood cultures subsequently grow *E coli* sensitive to cipro, TMP-Sulfa and gentamicin.



Questions 2

- How does Diabetes impact UTIs?
- How is simple cystitis managed?
- How do you treat pyelonephritis?
- How do you manage emphysematous UTIs?

Impact of DM on Urinary Tract Infection

- Diabetics have a higher incidence of bacteriuria (2 to 4-fold)
- The upper urinary tract is involved in 80% of diabetics with UTI
- Complications of UTI in diabetics include:
 - Perinephric abscess
 - Renal abscess
 - Papillary necrosis (manifest as flank and abdominal pain)
 - Emphysematous cystitis/pyelonephritis

Cystitis (derived from archived 2011 IDSA UTI guidelines)

- Women, not pregnant, uncomplicated UTI
 - Nitrofurantoin Macrocrystals 100 mg po bid x 5 days
 - Now OK to use in the elderly if eGFR > 30
 - Trimethoprim/Sulfa → E coli now greater than 20% resistant to this drug in some Areas
 - Keflex 500 mg po bid for 7 days. (inferior to nitrofurantoin and TMP/Sulfa)
 - **Avoid using Quinolones** → creates resistance and selects for C difficile → Collateral Damage
- Men
 - Ciprofloxacin 500 mg po bid for 10 days
 - TMP-sulfa DS 1 po bid for 10 days

Pyelonephritis

- Outpatient, not pregnant
 - Ciprofloxacin 500 mg po bid
 - Consider giving a single dose of Gentamicin 5 mg/kg or Ceftriaxone 1gm IV
- Inpatient, ward patient
 - Ceftriaxone 1-2 gms IV daily
 - Ciprofloxacin 400 mg IV q 12h
- Inpatient, ICU case or Health Care Acquired
 - Pip-Tazo 4.5 gm IV q 6h
 - Add Gentamicin 5 mg/kg IV q 24h if in shock

Pyelonephritis Part 1

- Special Consideration
 - Treat non-diabetics for 7 days and **diabetics for 7-14 days**
 - Treat 14-28 days if there is abnormal anatomy:
 - Abscess or lobar nephronia
 - Stone
 - Transplanted kidney
 - Rule out prostatitis with rectal exam for men with UTI
 - The average time to defervesence is 4 days

Pyelonephritis Part 2

- Consider renal imaging with US or CT if
 - Fever persists over 4 days
 - Bacteremic or hypotensive
 - Renal failure present with possible obstructive uropathy
 - History of nephrolithiasis
- Patients who are doing well can be converted early on to oral quinolone therapy or Trimethoprim-Sula if doing well even if bacteremic as long as the organism is sensitive

Emphysematous UTI

- Epidemiology
 - Diabetes is the risk factor for most cases.
 - Most are women over age 60
- Pathophysiology
 - Elevated glucose levels in blood lead to production CO₂, H₂, N₂, and O₂
- Two syndromes:
 - Emphysematous cystitis:
 - air in the bladder wall → Treat 10 days
 - Emphysematous pyelonephritis
 - IV antibiotics are a must
 - Percutaneous drainage if moderately severe and nephrectomy for severe disease

Photograph 3



Case Presentation 4

A 39 year old man with a history of obesity with a BMI of 29 is admitted to the hospital with severe COVID-19. He requires 4 liters of nasal canula oxygen and dexamethasone therapy. While on steroids he required large doses of insulin to control his blood glucose level. He is eventually discharged home on glargine insulin 20 units daily plus preprandial regular insulin.

Does COVID-19 cause DM in children?

- Risk for Newly Diagnosed Diabetes > 30 Days After SARS-CoV-2 Infection among Persons Aged < 18 year. *Barrett et al, MMWR Jan 14, 2022/Vol 71/No.2*
- **Analyzed claims for patients with COVID-19 in**
 - **IQVIA database: patients with COVID-19 diagnosis 3/1/2020-2/26/2021**
 - **Health Verity database: patients with any encounter possibly related to COVID 2/2020-6/2021**
- Hazard ratio for new DM diagnosis was
 - 2.66 (IQVA) compared with nondiabetics
 - 1.31 (HealthVerity) compared with nondiabetics
- Hazard ratio for new DM diagnosis was 2.16 in IQVIA cohort c/w pre pandemic non-COVID acute respiratory illness patients
 - <https://www.cdc.gov/mmwr/volumes/71/wr/mm7102e2.htm>

How about in Adults? Newly diagnosed diabetes vs Pre-existing Diabetes Upon Admission for COVID-1

- *Cromer et al, J of DM and Its Complications, 2022*
 - Reviewed 1902 adult admissions for COVID at Mass General 3/1/20-9/27/20
 - Used **A1c > 6.5% or ICD coding to define pre-admission DM and glucose > 300 to define new DM** in previously undiagnosed patients
 - 594 likely had DM and 77 had new DM (45% of total)
 - 42.9% of those with new DM had a history of prediabetes before admission
 - **New DM were younger, less likely to be non-Hispanic White, and to have HTN, CAD, CHF, and CKD**
 - **New DM patients had lower random glucose and A1c but higher CRP, ferritin, LDH, AST & ALT**
 - Stress hyperglycemia is suggested as the likely mechanism
 - Half had regression of DM at follow-up
 - <https://pubmed.ncbi.nlm.nih.gov/35148936/>

Diabetes and COVID-19: A Bidirectional Relationship Review by *Unnikrishnan and Misra, Eur J Clin Nutrition, 2021 – Part 1*

- Diabetics are not more likely to be infected with SARS-CoV-2
- Diabetics have an increased risk of severe disease, pneumonia, ICU admission, mechanical ventilation and death
- Poor pre-admission glycemic control predicts poor outcome
- Prediabetics have increased risk of complications (3-fold)
- Risk of ICU admission highest for new diabetics

Diabetes and COVID-19: A Bidirectional Relationship Review by *Unnikrishnan and Misra, Eur J Clin Nutrition, 2021 – Part 2*

- Effect of COVID19 on hyperglycemia
 - Direct virus mediated beta-cell damage in the pancreas via ACEI receptor
 - Autoimmunity triggered by virus is less likely (takes months for other viruses)
 - Host inflammatory response
 - Iatrogenic hyperglycemia from steroids (RECOVERY trial)
- Pandemic effects: no exercise and no access to healthy food

<https://pubmed.ncbi.nlm.nih.gov/34163019/>

Other COVID-19/Diabetes Considerations

- DM is an indication for Rx of outpatients with mild COVID-19
 - Paxlovid po bid for 5 days (if within 5 days of symptom onset)
 - Remdesivir IV for 3 days (if within 7 days of symptom onset)
 - Bebtolovimab IV x 1 (if within 7 days of symptom onset)
- Remember to look up drug-drug interactions with Paxlovid
 - Statins
 - Clopidigrel
 - Amlodipine
 - Amiodarone

Photograph 4

