In This Section

V. Antibiotic Stewardship and Preventing/Reducing Multidrug Resistant Organisms

Introduction to Antibiotic Stewardship

Antimicrobial stewardship efforts aim at optimizing use of antimicrobials by improving selection, dose, duration, and route of administration of antimicrobials.[1] It is important to recognize that the role of antimicrobial stewardship efforts is not always to discontinue antimicrobials, but to optimize their use weighing risks and benefits. Diagnostic stewardship means optimizing selection of the appropriate test for the appropriate patient that would improve management, including antimicrobial selection.[2,3] Antimicrobial and diagnostic stewardship and infection prevention complement each other. Prolonged and broad-spectrum antibiotic exposure is associated with increased risk of invasive candidiasis and infection with multidrug resistant bacteria in neonates.[4,5] Newborns, especially preterm newborns, are at high risk for infection, and antibiotics are the most commonly prescribed medications in the NICU.[6] Applying diagnostic stewardship to diagnose and treat hospital acquired infections improves accuracy of surveillance of these infections and use of appropriate therapy

when indicated. Lastly, antibiotic use has been found, in observational studies, to be associated with worse outcomes in extremely low birth weight infants including increased incidence of necrotizing enterocolitis and death.[7, 31, 32]

POTENTIALLY BETTER PRACTICE

Establish a Multidisciplinary Collaborative Approach to Diagnostic and Antimicrobial Stewardship

Background, Rationale, and Goals

- Creating a culture change in antimicrobial and diagnostic stewardship is important [8]
- Empowering stewardship leadership style which is inclusive and enabling of frontline clinicians, compared to a controlling and supervision-driven style, results in decreased broad-spectrum antimicrobial use and decreased hospital acquired infections in the NICU and pediatric ICU (PICU) [9]
- Nursing involvement in stewardship efforts in critical care settings is essential and underutilized.10 The role of nurses in stewardship is likely more critical in NICU settings given nurses' distinct involvement in the direct care of neonates [33]

Recommended Guidelines and Algorithms

- A multidisciplinary stewardship team involves representation from advanced practice providers, nurses, pharmacists and physicians[11]
- Multidisciplinary team members update colleagues on new policies and guidance and encourage adoption of stewardship practices and interventions
- Identify a team leader who is accountable for NICU outcome measures relating to stewardship efforts
- Multidisciplinary interventions may include the following:[11]
  - **Antimicrobial time-out**: Facilitate an antibiotic time-out during rounds. This includes revisiting the indication, choice, and duration of antimicrobials at a specific interval after initiating therapy.
  - **Assuring appropriate diagnostics**: Examples include obtaining blood cultures before empiric antibiotic therapy is started, and obtaining sterile urine samples for cultures

Guidance on Quality and Process Improvement

- Identify "stewardship champions" from each of the following disciplines: nursing, pharmacy, advanced practice providers and physicians
- Conduct meetings involving the multidisciplinary stewardship team at regular intervals to discuss stewardship outcome measures, opportunities for improvement, and future directions
- Create an Antibiotic Utilization Review Committee to review selected cases (criteria may be prolonged antibiotics or broad-spectrum antibiotics, as examples) as a methodology to learn from patient cases

Outcome, Balancing and Process Measures

- Administration of antibiotics within one hour after the order is placed

POTENTIALLY BETTER PRACTICE

Measure the Effectivness of Diagnostic and Antimicrobial Efforts in the NICU

Background, Rationale, and Goals

- Antimicrobial use is variable among California NICUs independent of proven infection[12]
- Measuring the success of diagnostic and antimicrobial stewardship could be achieved by tracking antimicrobial use as well as safety and quality metrics
- Measuring antimicrobial use is important not only to evaluate the present state of antimicrobial use in comparison to peers and the success of diagnostic and stewardship efforts, but also to discover potential areas of improvement
- All California Children's Services approved NICUs are required to report antimicrobial use rate (AUR) to CPQCC[12]
- All participating CPQCC NICUs are required to report newborn antibiotic exposure (NAE), NEC, and late-onset-sepsis[13]
- Days of therapy (DOT) per 1000 patient days is another measure of antimicrobial use that is widely utilized in pediatrics[14]

Recommended Guidelines and Algorithms

- Measure at least one metric of antimicrobial use, such as AUR, NAE and/or DOT and post data for all healthcare providers to view
- Compare antimicrobial use metric to other NICUs of similar size and level of care
- Measure and follow the specific antimicrobial use of high-impact antimicrobials. This could include broad-spectrum, nephrotoxic, or high-cost antimicrobials.
- Compare antimicrobial use metric over time to determine the effectiveness of a targeted diagnostic or antimicrobial stewardship effort
- Consider measuring quality metrics that could potentially be affected by stewardship efforts such as nosocomial infections with multidrug resistant organisms,[15] acute kidney injury,[16] or NEC[7,17]
- Evaluate safety outcomes and balancing measures related to diagnostic or antimicrobial stewardship efforts such as mortality from newborn sepsis, hospital readmission and rate of restarting antimicrobials[17]

Outcome, Balancing and Process Measures

- AUR is the total number of patient-days that infants were exposed to one or more antibacterial or antifungal agents (antivirals are not included) administered intravenously or intramuscularly per 100 patient-days in the reporting NICU, expressed as a percentage[12,13]
- NAE is the number of newborns who received at least one dose of intravenous or intramuscular antibacterial or antifungal agents per 100 newborns. Both the numerator and denominator include all admitted newborns after maternal delivery, including those born outside the hospital but who received their initial medical evaluation at the hospital in question and newborns taken care of in mother/baby units[13]
- DOT per 1000 patient days is the number of days a patient receives a certain antimicrobial, or a group of antimicrobials divided by the number of hospital days. The numerator usually captures each antibiotic separately; for example, if a patient receives ampicillin and gentamicin for 7 days, she will have 14 DOTs. The denominator usually captures the census of a given population (for example: neonates) at 23:59.[14]
- Other safety and quality metrics may be related to diagnostic and antimicrobial stewardship efforts include: multidrug resistant nosocomial infections,[15] NEC rates,[7] hospital readmissions, rate of fungal late-onset sepsis, rate of restarting antimicrobials, mortality from newborn sepsis and episodes of acute kidney injury associated with nephrotoxic antimicrobials[16,18,19]

POTENTIALLY BETTER PRACTICE

Develop Antimicrobial and Diagnostic Stewardship Interventions

Background, Rationale, and Goals

- Consider multiple interventions to improve appropriate use of diagnostics and antimicrobials.[14,20] These interventions may include antimicrobial restriction, audits and feedback, provider education, optimizing diagnostics, development of clinical pathways, infection prevention efforts and antibiotic time-outs and automatic stop orders[3,14,20,21]

Recommended Guidelines and Algorithms

- Define goals and opportunities for improvement by reviewing NICU-specific antimicrobials as compared to NICUs of similar size, at least annually
- Goals include optimizing antimicrobial use of a specific broad-spectrum or toxic antimicrobial, optimizing antimicrobial use for a specific indication, gestational age groups (example: >35 weeks) or timing of neonatal sepsis (early-onset or late-onset), or general reduction in antimicrobial use
- Consider prospective audits and feedback whenever resources are available[14,22,23]
- Consider preauthorization for targeting specific broad-spectrum, highly toxic and/or excessively used antimicrobials[14]
- Establish diagnostic criteria or guidelines when there are concerns for over diagnosis of a specific infection based on the rate of this infection in comparison to other NICUs[3,21]
- Establish treatment guidelines if there are concerns for prolonged treatment of specific diagnoses[17]
- Implement provider education as an adjunctive measure to other interventions[14,22,24]

Outcome, Balancing and Process Measures

- AUR and NAE in comparison to other NICUs within CPQCC
- DOT per 1000 patient days for specific antimicrobials or diagnoses
- NEC, ventilator associated pneumonia, CLABSI, urinary tract infection and coagulase negative *Staphylococcus* infection rates

POTENTIALLY BETTER PRACTICE

Develop Clinical Pathways and Guidelines for Common Neonatal Infections

Background, Rationale, and Goals

- Developing clinical pathways and guidelines is an effective strategy for improving diagnostic and antimicrobial stewardship[24–26]
- Clinical guidelines provide consistency in clinical practice, which might improve communication among medical providers and between medical providers and families. Consistency in clinical practice could also help detect adverse outcomes when care deviates from specific guidelines or practices.
- Higher blood volumes obtained for blood culture correlate with higher sensitivity and lower contamination rates[27]

Recommended Guidelines and Algorithms

- Develop unit-specific diagnosis and treatment guidelines to help standardize the approach to:
  - Early onset infection in the term and preterm infant
  - Late onset infection
  - Necrotizing enterocolitis
  - Culture negative sepsis and pneumonia[17]
  - Ventilator associated pneumonia[21]
  - Urinary tract infection
- Develop perioperative prophylaxis antibiotic guidelines specific to the NICU to reduce variability in prophylactic antibiotic choice and duration[28]
- Adopt a standardized blood culture process, including minimum blood volume for blood culture of **at least** 1 ml[3,27]
- Avoid routine endotracheal aspirate cultures to rule out sepsis when ventilator associated lower respiratory infection is not suspected based on other clinical considerations[21,29,30]
- Avoid a diagnosis of ventilator associated pneumonia (VAP) based on endotracheal aspirate cultures. Rather, use endotracheal aspirate culture results to support the diagnosis of VAP in inconclusive cases or to guide antimicrobial therapy for diagnosed VAP based on clinical and imaging criteria[21,29,30]
- Use vancomycin for empiric antibiotic coverage for late onset sepsis only if methicillin resistant *Staphylococcus aureus* (MRSA) infection rates are high[3,24]
- Monitor blood culture contamination data and develop standardized approach to blood culture collection techniques[34-36]

Outcome, Balancing and Process Measures

- Compliance with unit-specific diagnosis and treatment guidelines
- Possible balancing measures could include mortality, surgical site infection, recurrent infection, or restarting antimicrobials

Introduction to Multidrug Resistant Organisms

Multidrug resistant organisms (MDROs) are microorganisms that are resistant to one or more antimicrobials.[1] Although most of these organisms are bacteria, including MRSA, vancomycin resistant Enterococcus (VRE), and multi-drug resistant gram-negative rods (MDR-GNR), they also include fungi such as *Candida auris*.[2] The causes of antimicrobial resistance, and the resultant spread of MDROs, are complex, but include increased antimicrobial use in the care of people, animals and crops.[3,4] MDROs cause more than 2.8 million infections and more than 35,000 deaths in the United States each year.[3] Further, MDROs can cause outbreaks in the NICU, resulting in significantly increased length of stay and cost of care.[5] *Staphylococcus aureus* outbreaks in the NICU are common and it is imperative that NICUs take precautions and develop policies to prevent spread.[20]

POTENTIALLY BETTER PRACTICE

Implement Measures to Recognize and Prevent Staphylococcus Aureus Infection in the NICU, Including Methicillin Resistant Staphylococcus Aureus (MRSA)

Background, Rationale, and Goals

- MRSA is *Staphylococcus aureus* with resistance to methicillin and other anti-staphylococcal penicillins due to a change in the structure of the penicillin binding receptor
- There are controversies and variations in practice regarding the requirement for MRSA screening upon admission for inborn NICU patients[6]
- Studies evaluating decolonization protocols for *Staphylococcus aureus* have mixed results for decreasing infection and colonization with *Staphylococcus aureus*[7,8]
- It is likely that no one standalone intervention will decrease infection and colonization with *Staphylococcus aureus*; rather, a multi-intervention bundle, including ensuring compliance with basic and standard infection prevention practices, is required[9,10]

Recommended Guidelines and Algorithms

- There is no specific standard or guideline for frequency of active or periodic surveillance for *Staphylococcus aureus* if the rate of *Staphylococcus aureus* infection is low[21]
- NICU patients colonized with MRSA have an increased risk of developing MRSA infection and decolonization may reduce this risk. However, an optimal decolonization protocol for NICU patients has not been identified.[9, 22] Routine decolonization or active periodic surveillance for *Staphylococcus aureus* in non-outbreak settings is not recommended[9]
- Recommendations for contact precautions on all neonates who are colonized with MRSA without evidence of infection are mixed.[11] However, these measures are commonly used as a part of a multi-intervention strategy to control healthcare associated MRSA transmission, during MRSA outbreaks, and especially in high-risk settings such as the NICU[1,9,19, 22, 23]
- High levels of hand hygiene compliance may not be enough to stop the spread of MRSA; additional complimentary precautions such as cohorting, contact isolation, and decolonization are needed[23, 24]
- Implement contact precautions for neonates with MRSA infection
- Other interventions recommended in cases of *Staphylococcus aureus* outbreaks or high infection rate:[7,9,19]
  - Focused hand hygiene interventions to assure and improve compliance
  - Cleaning and disinfection of NICU common areas and development of an ongoing cleaning protocol of high touch/common areas and equipment performed by NICU staff and/or combination of technicians and staff
  - Dedicated single-patient equipment (e.g., thermometer, blood pressure machine, mobile computer, diaper scale, etc.)
  - Contact precautions for neonates colonized with MRSA
  - Active surveillance of all NICU patients, consider weekly throughout hospitalization[19]
  - Decolonization of *Staphylococcus aureus* or, more specifically, MRSA
  - Staff cohorting and changing staffing ratios
  - Staff screening and decolonization may be considered; staff with chronic skin conditions may need special attention as they may continue to harbor S. aureus[24]
- If decolonization is used, mupirocin ointment, two nasal applications daily for five days, and selected patient bathing with chlorhexidine may be cautiously considered, based upon patient's risk of MRSA invasive disease.[7,8, 9, 19]
- Inform local public health partners of MRSA outbreaks and use their expertise for case identification and infection control

Outcome, Balancing and Process Measures

- Rate of MRSA colonization per admission or, if periodic screening is performed for outbreaks, over time per 1000 patient days
- Rate of *Staphylococcus aureus* and, more specifically, MRSA infections. This could be categorized by infection site such as bloodstream and skin and soft tissue infections[7]

POTENTIALLY BETTER PRACTICE

Take Measures to Identify and Control Multidrug Resistant Gram-Negative Rods

Background, Rationale, and Goals

- Multidrug resistant Gram-negative rods (MDR-GNR) are a broad group of bacteria that includes, extended spectrum beta-lactamase producing Enterobacterales (ESBL-E), carbapenem resistant Enterobacterales (CRE), and other Gram negative bacteria that have inherent or acquired resistance to multiple classes of antibiotics[1]
- MDR-GNR infections are difficult to treat and associated with high morbidity and mortality[3]
- ESBL-E are ubiquitous and increasing in prevalence in the community and healthcare settings.[12,13] They are known to cause outbreaks in the NICU[14]
- The role of surveillance and contact precautions for ESBL-E is controversial[13,15–17]

Recommended Guidelines and Algorithms

- For identification, define the different groups of MDR-GNR as follows:
  - **ESBL-E:** Enterobacterales resistant to at least one third generation cephalosporin[18]
  - **CRE:** Enterobacterales that are resistant to at least one carbapenem or producing a carbapenemase enzyme[18]
  - ***Burkholderia cepacia, Stenotrophomonas***

maltophilia,* and *Ralstonia pickettii are inherently resistant to broad antibiotics and are thus all considered MDROs[1]
    - **Other MDR-GNR such as *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and Enterobacterales** that do not meet the above criteria: definition is variable between institutions depending on infection prevention and control policies
- Follow hospital policy regarding screening and contact precautions for ESBL-E. Controversies exist regarding optimal interventions to prevent the spread of ESBL-E.[13,15–17] These interventions should be reserved to outbreak settings given the high prevalence of ESBL-E as commensals,[12] and that evidence for surveillance and isolation comes from quasi-experimental studies which are inherently biased.[13]
- Contact precautions are recommended for all other MDR-GNRs as well as relying on the local infection prevention and control team for duration of isolation
- Inform the local public health partners of MDR-GNRs outbreaks and use their expertise for case identification and infection control

Guidance on Quality and Process Improvement

- Develop and implement a NICU-specific MDRO policy that outlines care practices including isolation requirements, treatment guidelines, and family activities
- Assure hospital systems are in place to identify and flag cultures that are positive for MDR-GNRs
- Review all infections due to MDR-GNRs to identify potential trends and commonalities
- In outbreak settings, review compliance with surveillance and control measures

Resources and Tools

Tools

The following tools are included in this section:

1. Obtaining a Blood Culture Checklist
2. Early-Onset Sepsis (EOS) and Late-Onset Sepsis (LOS) Algorithms
3. Antibiotic Time Out Sheet

OBTAINING A BLOOD CULTURE CHECKLIST - PAGE 1

SOURCE: University of California, Irvine (UCI) Health

UCI Health

Blood Culture Checklist

Peripheral Blood Culture

Obtain Supplies

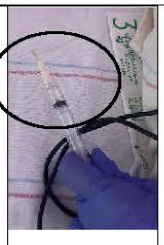
23-25 gauge butterfly (depending upon size of patient)	alcohol prep pad	White chux (to protect from bed linens)
blood culture bottle and transfer device	Exidine (CHG) skin prep	sterile gloves
3-5 ml syringe (depends upon volume of other labs)	sterile 2X2	normal saline wipe

Steps

1	Verify MD Order	
2	Obtain oral sucrose for pain	
3	Check expiration on blood culture bottle	
4	Verify correct patient identification by comparing blood culture order to patient's medical record number and name on patient band	
5	Cleanse overbed table with disinfectant	
7	Open all sterile supplies using cleansed overbed table as work surface; pour small amount of Exidine onto sterile 2X2	
8	Wash hands and immobilize patient; protect eyes from exam light; obtain assistance (this is a two-person procedure)	
9	Place white chux underneath extremity to prevent contamination from bed linens	
10	Wash hands again	
11	Using sterile gloves, connect syringe to end of butterfly. Prep skin using sterile 2X2 with Exidine; apply using a forward, backwards and side to side cleaning motion. Allow to dry for 30 seconds.	
12	Perform venipuncture (or arterial stick); **obtain 1 mL for blood culture for ALL infants**	
13	After obtaining the sample, activate the safety needle device.	
14	Prior to inoculation, scrub top of blood culture bottle with alcohol wipe prior to transferring blood into blood culture bottle	
15	Hand syringe to assistant to inoculate blood into blood culture bottle.	
16	Transfer blood culture specimen to blood culture bottle using the blood transfer device	
17	Cleanse skin area with NS wipe to remove Exidine	
18	Dispose of all sharps in sharps container	
19	Gently invert bottle 2-3 times	
20	Label culture bottle using electronic lab collection system (Rhodes); alternatively, if electronic labeling system unavailable, label with patient sticker and note on sticker if collection site is peripheral or central and send with transmittal	
21	Document lab draw in EMR	

Place white chux underneath site to protect from contamination; cleanse using Exidine and allow area to dry before performing collection.

Connect the syringe to the end of the butterfly tubing to reduce contamination during sampling



After scrubbing the top of the blood culture bottle with alcohol swab, use the blood transfer device to inoculate the blood culture bottle

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OBTAINING A BLOOD CULTURE CHECKLIST - PAGE 2

SOURCE: University of California, Irvine (UCI) Health

UCI Health

Blood Culture Checklist

Central Line Blood Culture (PICC/Broviac)

Note: blood culture samples are not routinely drawn from umbilical lines as part of a late onset sepsis work-up; only use umbilical line for blood culture when the umbilical line is immediately placed

Obtain Supplies

Sterile Gloves	Alcohol prep pad X2	White chux (to protect from bed linens)
Blood culture bottle and transfer device	3-5 ml syringe	

Steps

1	Verify MD Order	
2	Check expiration on blood culture bottle	
3	Verify correct patient identification by comparing blood culture order to patient's medical record number and name on patient band	
4	Cleanse overbed table with disinfectant	
5	Open all sterile supplies using cleansed overbed table as work surface	
7	Turn IV pump to stand-by	
8	Place white chux underneath extremity or connection of clave to IV tubing to prevent contamination from bed linens	
9	Wash hands again	
10	Don sterile gloves: scrub the tubing vigorously with alcohol pad where the clave attaches to the main IV tubing; this is the area that will be disconnected (disconnect the IV tubing at the clave; do not remove clave to draw blood); scrub for 30 seconds.	
11	Disconnect IV tubing keeping IV tubing end protected (hand to assistant) and scrub end of clave with alcohol vigorously for 30 seconds. Assure the end of the IV tubing remains protected and sterile.	
12	Attach syringe to clave and withdraw 1 ml (no discard needed for any central line)	
13	Prior to inoculation, scrub top of blood culture bottle with alcohol wipe prior to transferring blood into blood culture bottle	
14	Hand syringe to assistant to inoculate blood into blood culture bottle.	
	Re-connect IV tubing to clave; no flush is required to the central line (PICC/Broviac) unless line is heparin locked. If heparin locked, flush line per MD order.	
15	Gently invert bottle 2-3 times	
16	Label culture bottle using electronic lab collection system (Rhodes); alternatively, if electronic labeling system unavailable, label with patient sticker and note on sticker if collection site is peripheral or central and send with transmittal	
17	Restart IV pump	
18	Document lab draw in EMR	
19		
20		

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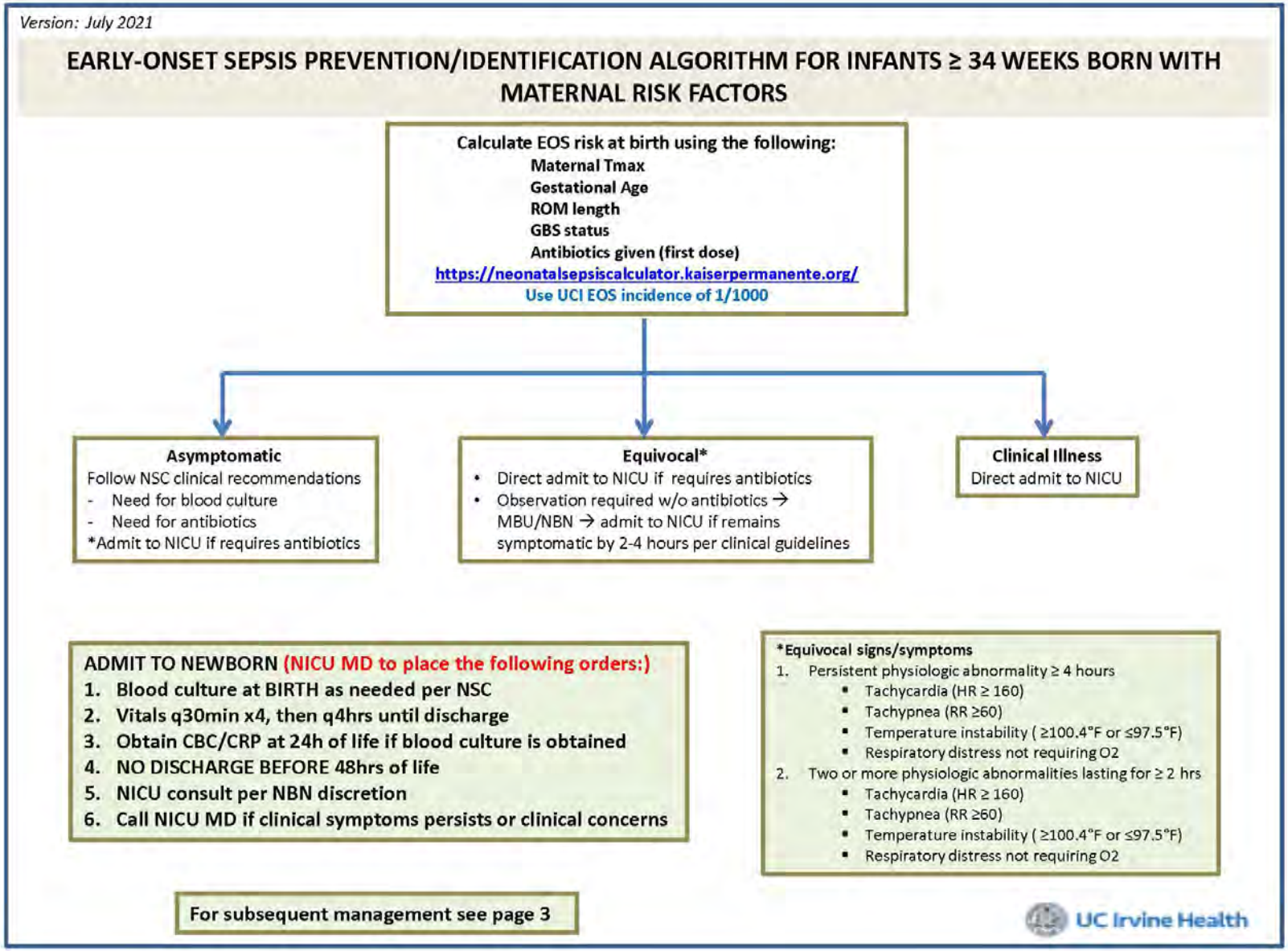
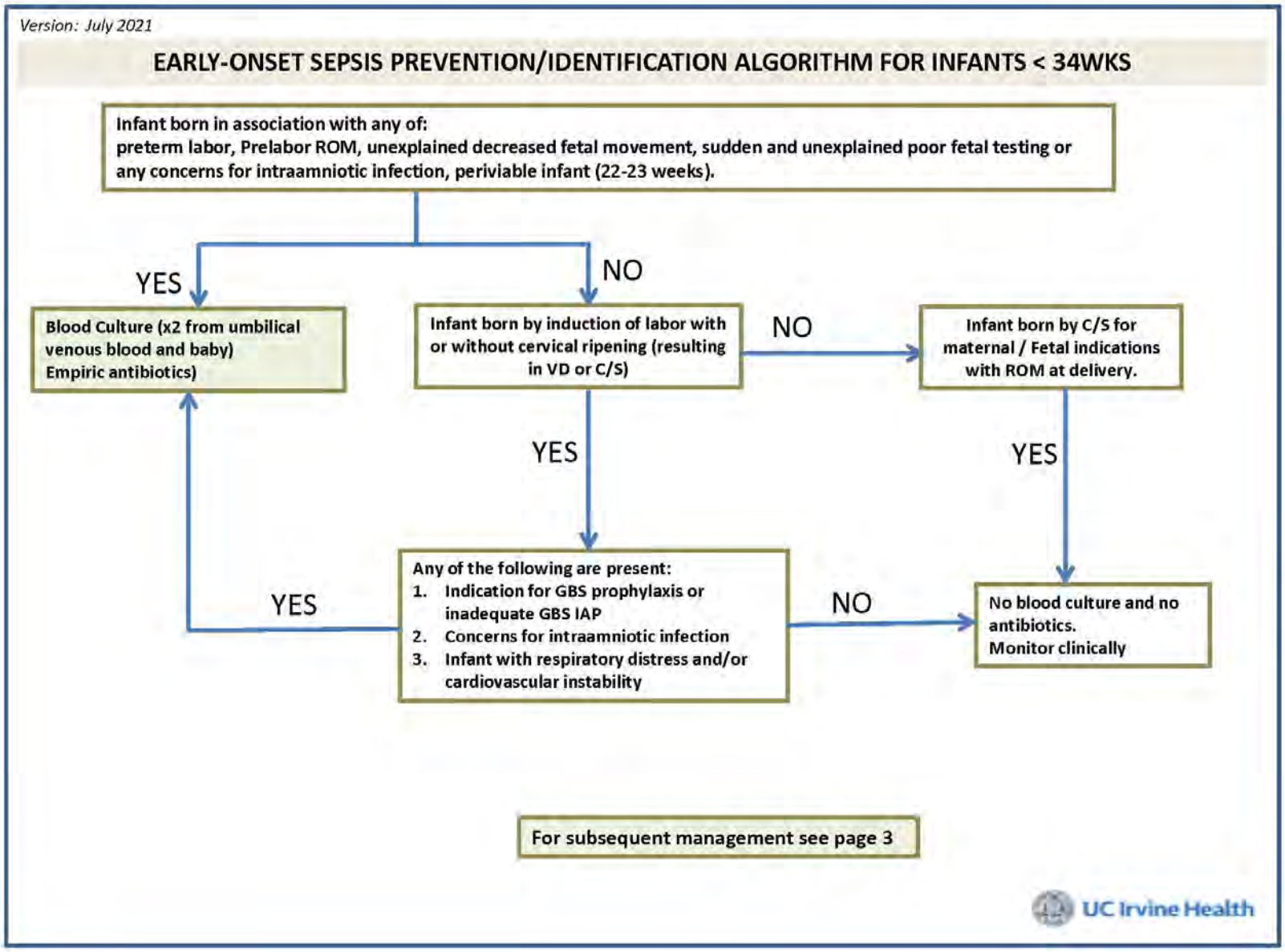
EARLY ONSET SEPSIS (EOS) ALGORITHM - PAGE 1

SOURCE: University of California, Irvine (UCI) Health



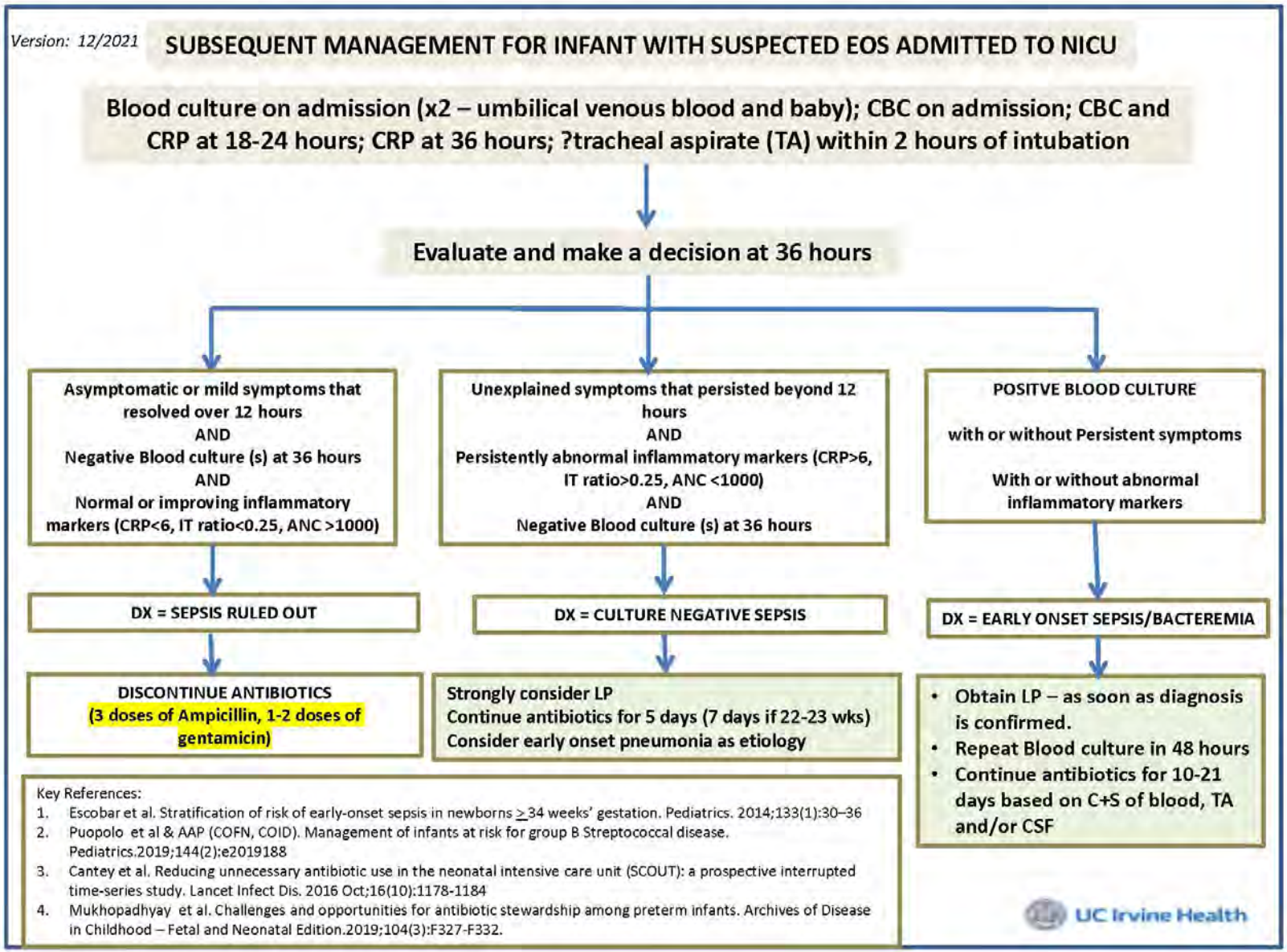
EARLY ONSET SEPSIS (EOS) ALGORITHM - PAGE 2

SOURCE: University of California, Irvine (UCI) Health



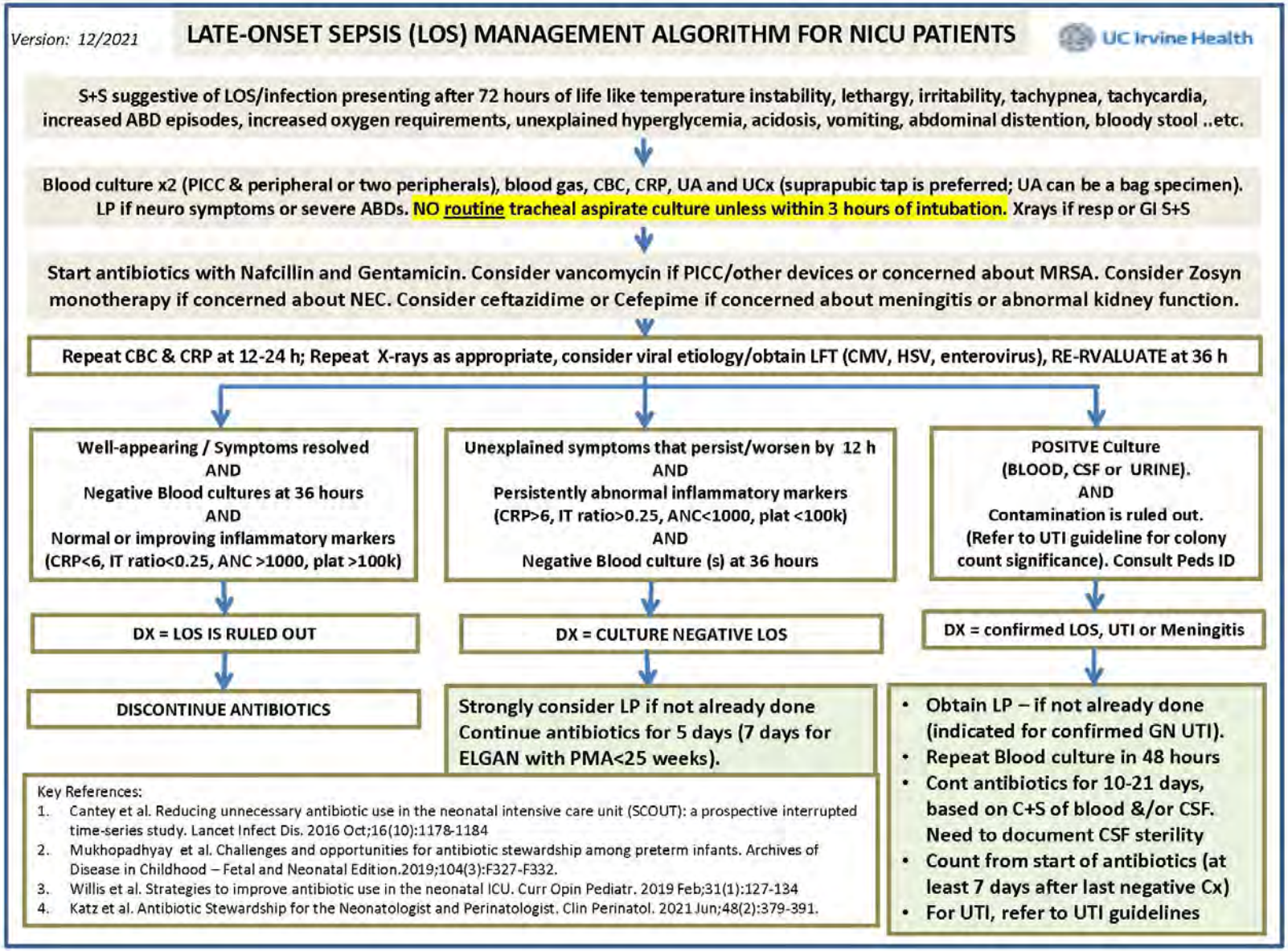
EARLY ONSET SEPSIS (EOS) ALGORITHM - PAGE 3

SOURCE: University of California, Irvine (UCI) Health



LATE ONSET SEPSIS (LOS) ALGORITHM

SOURCE: University of California, Irvine (UCI) Health



DAILY ANTIBIOTIC TIME OUT SHEET

SOURCE: University of California, Irvine (UCI) Health

Daily Antibiotic Time Out

Patient Name	Antibiotics Receiving/Dose/Frequency	Medical Plan for Antibiotics Guidelines Used	Interventions 1= clarifying indication for treatment 2= determining duration of treatment 3=Enter future stop dates 4= de-escalate 5=dosage adjustment/drug levels

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