Antibiotics in ICU; trials & tribulations

When to culture a narrow mindset

Nepean WTET summary 20/10/20

Background and Rationale

- Severe sepsis and septic shock remain amongst our most common admission diagnoses to ICU and continues to be associated with high morbidity and mortality despite advances in critical care medicine. Antibiotics (Abx) form a key part of ICU practice in this regard
- Whilst minimally invasive as far as a treatment goes, consequences of inappropriate vs delayed, broad vs narrow and under vs over-dosing of antimicrobial therapies exist
- Furthermore unlike other pathologies (e.g. CVA), infectious diseases themselves are evolving…

Advantages and Disadvantages

- Advantages of liberal approach
    - We are still reasonably far away from having bedside testing that allows rapid detection of culprit organisms. Cultures and sensitivities (and even currently PCR) take time. Too narrow too soon may miss treating the appropriate pathogen and lead to treatment failure and deterioration. Gram stains (alongside a clinical picture) may assist to some extent
    - Multiresistant organisms (MROs) are becoming increasingly common. Whilst 'broad spectrum Abx' might select out resistance, in critically ill, failure to treat is also problematic
- Disadvantages of liberal approach
    - This may induce resistance to last line antibiotics e.g. rationale for MERINO trial; broad use of carbapenems for extended-spectrum b-lactamase (ESBL) producing enterobacteriaceae may select out carbapenem resistance; ?is piperacillin-tazobactam (tazocin) noninferior?
    - Disruption of usual flora and implications for opportunistic overgrowth of other organisms

Key studies

- WHEN
    - Kumar 2006 Crit Care Med
        - MC retrospective review (14 ICUs in CA/US, varying time span of data provided, but range from 07/1989 – 06/2004) patients with septic shock (SCCM/ACCP 1991 definition). N=2731 (58.1% community-acquired, 41.9% nosocomial)
        - Over first 6h, onset of recurrent or persistent hypotension, each hour delay in initiation of effective antimicrobial therapy was associated with mean decrease in survival of 7.6%. Multivariate analysis (incl. APACHE) found time to initiation of effective antimicrobial therapy was single best predictor of outcome ($P<0.001$)
        - Documented infections in 77.9% with remaining 22.1% having suspected infections without plausible bacterial pathogen on radiological, surgical, autopsy or biopsy
    - Sterling et 2015 Crit Care Med
        - SR & MA; 18 studies eligible however sufficient data available from only 11 (all moderate-high quality; included Kumar). N=16178
        - No significant mortality benefit of administering Abx <3h of ED triage or <1h of severe sepsis or septic shock

- WHERE
    - Cochrane review; 2018
        - 57 studies = 16748 central venous catheters and 11 types of impregnations
        - Impregnation ARR of catheter-related blood stream infection (CRBSI) of 2% and catheter colonisaion of 9%. With no difference in mortality or sepsis. However there was significant heterogeneity (included oncology and long term parenteral nutrition patients, not just ICU patients). Reduction of CRBSI was particularly of note in haem/onc/ICU population (not TPN). No difference in adverse events
- WHAT
    - MERINO trial; 2018 JAMA
        - MC RCT (open label) non-inferiority; Blood stream infection caused by ceftriaxone-nonsusceptible, tazocin-sensitive E coli or Klebsiella. Stratified by species (E-coli vs klebsiella), infection source (urinary tract vs other) and severity of disease (Pitt bacteraemia score =/<4 vs >4). Randomised to tazocin 4.5g TDS or meropenem 1g TDS. All had blood cultures at d3 (or if febrile >38^{o}C) up until d5. N=379
        - Primary outcome; all-cause mortality at 30d; 12.3% tazocin vs 3.7% meropenem (also had higher APACHE) P=0.90 for non-inferiority (i.e. tazocin is not non-inferior)
- HOW
    - BLING 2 trial; 2015 Am J Resp & Crit Care Med
        - MC DB RCT; Severe sepsis commenced on tazocin, ticarcillin-clavulanate (timentin) or meropenem <24h, randomised to continuous infusion versus intermittent dosing (over 30mins) til cessation or discharge from ICU. N=432
        - Primary outcome; alive ICU-free days d28; 18 vs 20, P=0.38
        - Longer ICU LOS 7d vs 6d, P=0.042 with continuous infusion (unclear why)
        - Needs larger phase 3 RCT to see what subgroups may benefit… BLING 3
    - STOP-IT trial; 2015 NEJM
        - MC RCT (open-label); Complicated intraabdominal infection (fever, leucocytosis, GI dysfunction; secondary to peritonitis) requiring source control procedure. Randomised to 4d full antimicrobial therapy after source control procedure vs antimicrobial therapy til 2d post resolution of physiological abnormalities (SIRS; 1d without fever =/>38^{o}C, WCC <11000/mm^{3}, eating >1/2 normal diet without adverse effects). N=518
        - Primary outcome; surgical site infection, recurrent intraabdominal infection or death <30d of index source-control procedure;

Summary (my practice)

- Abx are seldom appropriately selected, prescribed and administered in isolation – a package of assessment, resuscitation, investigation and appropriate adjunctive therapies (e.g. source control and supportive therapies) likely contribute to survival in severe sepsis / septic shock (e.g. Kumar)
- Separating out delay to Abx from delay to appropriate +/- senior medical attention is difficult. On the-other-hand it is reasonable to not tolerate unnecessary delays in time to administration; no RCTs will be performed looking at timing to appropriate Abx use in this setting (septic shock)
- Appropriate Abx selection is key as early yet inappropriate Abx use (selection, dose, route) makes timing of administration irrelevant. In the absence of clear likely pathogen it is reasonable to start broad but narrow early (once organism +/- sensitivities known) in the critically ill
- Source control is key, and a short course of Abx often appropriate after source control achieved
- I use coated CVCs selectively in high risk ICU patients (prolonged need +/- high infection risk)
- Screening for MROs gives important information with regards to empirical cover for future deteriorations. Also important for minimising spread (infection control)
- I give Meropenem first line for ESBL even if tazocin sensitive on initial reported sensitivities
- With many patient factors affecting personal pharmacokinetics (and organism factors affecting MIC) in the critically ill, the future may well lie in therapeutic drug monitoring; I await DOLPHIN trial